

**UNITED STATES
SECURITIES AND EXCHANGE COMMISSION**
Washington, D.C. 20549
FORM 10-K

(Mark One)

☒ **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the fiscal year ended December 31, 2022

OR

☐ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934 FOR THE
TRANSITION PERIOD FROM TO**

Commission File Number 001-40505

Ambrex Biopharma Inc.

(Exact Name of Registrant as specified in its charter)

Cayman Islands
(State or other jurisdiction of
incorporation or organization)
10975 North Torrey Pines Road
La Jolla, California, United States
(Address of principal executive offices)

Not Applicable
(I.R.S. Employer
Identification No.)

92037
(Zip Code)

Registrant's telephone number, including area code: (858) 875-2400

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
American Depositary Shares (ADSs), each representing seven ordinary shares, par value \$0.0001 per ordinary share	AMAM	Nasdaq Global Select Market
Ordinary shares, par value \$0.0001 per share*		Nasdaq Global Select Market*

* Not for trading, but only in connection with the registration of the American Depositary Shares.

Securities registered pursuant to Section 12(g) of the Act: **None**

Indicate by check mark if the Registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ☐ No ☒

Indicate by check mark if the Registrant is not required to file reports pursuant to Section 13 or 15(d) of the Act. Yes ☐ No ☒

Indicate by check mark whether the Registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the Registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes ☒ No ☐

Indicate by check mark whether the Registrant has submitted electronically every Interactive Data File required to be submitted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the Registrant was required to submit such files). Yes ☒ No ☐

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, a smaller reporting company, or an emerging growth company. See the definitions of "large accelerated filer," "accelerated filer," "smaller reporting company," and "emerging growth company" in Rule 12b-2 of the Exchange Act.

Large accelerated filer	<input type="checkbox"/>	Accelerated filer	<input type="checkbox"/>
Non-accelerated filer	<input checked="" type="checkbox"/>	Smaller reporting company	<input checked="" type="checkbox"/>
		Emerging growth company	<input checked="" type="checkbox"/>

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☒

Indicate by check mark whether the registrant has filed a report on and attestation to its management's assessment of the effectiveness of its internal control over financial reporting under Section 404(b) of the Sarbanes-Oxley Act (15 U.S.C. 7262(b)) by the registered public accounting firm that prepared or issued its audit report. ☐

If securities are registered pursuant to Section 12(b) of the Act, indicate by check mark whether the financial statements of the registrant included in the filing reflect the correction of an error to previously issued financial statements. ☐

Indicate by check mark whether any of those error corrections are restatements that required a recovery analysis of incentive-based compensation received by any of the registrant's executive officers during the relevant recovery period pursuant to §240.10D-1(b). ☐

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). Yes ☐ No ☒

The aggregate market value of the registrant's voting and non-voting common equity held by non-affiliates, based on the closing price per share of ADSs on The New York Stock Exchange was approximately \$75.9 million as of June 30, 2022.

The number of shares of registrant's ordinary shares outstanding as of March 20, 2023, was 386,486,014.

DOCUMENTS INCORPORATED BY REFERENCE

As noted herein, the information called for by Part III of this Annual Report on Form 10-K is incorporated by reference to specified portions of the registrant's definitive proxy statement to be filed in conjunction with the registrant's 2023 Annual Meeting of Shareholders, which is expected to be filed not later than 120 days after the registrant's fiscal year ended December 31, 2022.

Auditor Firm Id:	34	Auditor Name:	Deloitte & Touche LLP	Auditor Location:	San Diego, California, United States
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AMBRX BIOPHARMA INC.
ANNUAL REPORT ON FORM 10-K
FOR THE YEAR ENDED DECEMBER 31, 2022

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GENERAL INFORMATION

Unless otherwise indicated or the context otherwise requires, all references in this Annual Report on Form 10-K, or Annual Report, to the terms "Ambrx," "Ambrx Biopharma," "the Company," "we," and "our" may refer, as the context requires, to Ambrx Biopharma Inc. or collectively to Ambrx Biopharma Inc. and its subsidiaries.

This Annual Report contains references to our trademarks and trademarks belonging to other entities. Solely for convenience, trademarks and trade names referred to in this Annual Report, including logos, artwork and other visual displays, may appear without the ® or ™ symbols, but such references are not intended to indicate, in any way, that we will not assert, to the fullest extent under applicable law, our rights or the rights of the applicable licensor to these trademarks and trade names. We do not intend our use or display of other companies' trade names or trademarks to imply a relationship with, or endorsement or sponsorship of us, by any other companies.

PRESENTATION OF FINANCIAL AND OTHER INFORMATION

Our consolidated financial statements have been prepared in accordance with accounting principles generally accepted in the United States of America, or U.S. GAAP.

Our functional currency is the U.S. dollar. Unless otherwise specified, all monetary amounts presented are in U.S. dollars.

We have made rounding adjustments to some of the figures included in this Annual Report. Accordingly, numerical figures shown as totals in some tables may not be an arithmetic aggregation of the figures that preceded them.

CAUTIONARY STATEMENT REGARDING FORWARD-LOOKING STATEMENTS

This Annual Report contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, or the Securities Act, and Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act, that involve substantial risks and uncertainties. In some cases, you can identify forward-looking statements by the words "may," "might," "will," "could," "would," "should," "expect," "intend," "plan," "objective," "anticipate," "believe," "estimate," "predict," "potential," "continue" and "ongoing," or the negative of these terms, or other comparable terminology intended to identify statements about the future. These statements involve known and unknown risks, uncertainties and other important factors that may cause our actual results, levels of activity, performance or achievements to be materially different from the information expressed or implied by these forward-looking statements. The forward-looking statements and opinions contained in this Annual Report are based upon information available to us as of the date of this Annual Report and, while we believe such information forms a reasonable basis for such statements, such information may be limited or incomplete, and our statements should not be read to indicate that we have conducted an exhaustive inquiry into, or review of, all potentially available relevant information. Forward-looking statements include statements about:

- the timing, progress and results of preclinical studies and clinical trials for our product candidates, including our product development plans and strategies;
- the timing, scope and likelihood of regulatory filings and approvals, including final regulatory approval of our product candidates;
- the potential benefits and market opportunity for our product candidates and technologies;
- expectations regarding the size, scope and design of clinical trials;
- our manufacturing, commercialization, and marketing plans and strategies;
- our plans to hire additional personnel and our ability to attract and retain such personnel;

- our estimates of the number of patients who suffer from the diseases we are targeting and potential growth in the patient populations;
- our expectations regarding the approval and use of our product candidates as first, second or subsequent lines of therapy or in combination with other drugs;
- our competitive position and the development and impact of competing therapies that are or may become available;
- expectations regarding future events under licensing and research and development agreements, including potential future payments, as well as our plans and strategies for entering into further licensing and research and development agreements;
- our intellectual property position, including the scope of protection we are able to establish and maintain for intellectual property rights covering product candidates we may develop, including the extensions of existing patent terms where available, the validity of intellectual property rights held by third parties, and our ability not to infringe, misappropriate or otherwise violate any third-party intellectual property rights;
- the rate and degree of market acceptance and clinical utility of our product candidates we may develop;
- our estimates regarding expenses, future revenue, capital requirements and needs for additional financing;
- our future financial performance;
- the period over which we estimate our existing cash, cash equivalents and marketable debt securities will be sufficient to fund our future operating expenses and capital expenditure requirements;
- the impact of laws and regulations; and
- by the effects of the ongoing COVID-19 pandemic, the ongoing conflict between Ukraine and Russia, bank failures and other geopolitical and macroeconomic conditions.

You should refer to the section titled “*Item 1A. Risk Factors*” for a discussion of important factors that may cause our actual results to differ materially from those expressed or implied by our forward-looking statements. As a result of these factors, we cannot assure you that the forward-looking statements in this Annual Report will prove to be accurate. Furthermore, if our forward-looking statements prove to be inaccurate, the inaccuracy may be material. In light of the significant uncertainties in these forward-looking statements, you should not regard these statements as a representation or warranty by us or any other person that we will achieve our objectives and plans in any specified time frame, or at all. We undertake no obligation to publicly update any forward-looking statements, whether as a result of new information, future events or otherwise, except as required by law. We claim the protection of the safe harbor for forward-looking statements contained in the Private Securities Litigation Reform Act of 1995 for all forward-looking statements.

You should read this Annual Report and the documents that we reference in this Annual Report, completely and with the understanding that our actual future results may be materially different from what we expect. We qualify all of our forward-looking statements by these cautionary statements.

Unless otherwise indicated, information contained in this Annual Report concerning our industry and the markets in which we operate, including our general expectations and market position, market opportunity and market size estimates, is based on information from independent industry analysts, third-party sources and management estimates. Management estimates are derived from publicly available information released by independent industry analysts and third-party sources, as well as data from our internal research, and are based on assumptions made by us based on such data and our knowledge of such industry and market, which we believe to be reasonable. In addition, while we believe the market opportunity information included in this Annual Report is generally reliable and is based on reasonable assumptions, such data involve risks and uncertainties and are subject to change based on various factors, including those discussed under the section of this Annual Report titled “*Item 1A. Risk Factors*.”

SUMMARY OF RISK FACTORS

Investing in our shares involves numerous risks, including the risks described in “*Item 1A. Risk Factors*” of this Annual Report. Below are some of our principal risks, any one of which could materially adversely affect our business, financial condition, results of operations and prospects:

- We have incurred net losses since our inception and anticipate that we will continue to incur significant losses for the foreseeable future. We may never generate any revenue or become profitable or, if we achieve profitability, may not be able to sustain it.
- We will need to obtain substantial additional funding to complete the development and commercialization of our product candidates. If we are unable to raise this capital when needed, we may be forced to delay, reduce or eliminate our product development programs or other operations.
- We are early in our development efforts and have a limited history of conducting clinical trials to test our product candidates in humans.
- Our business is highly dependent on our product candidates, and we must complete additional clinical testing before we can seek regulatory approval and begin commercialization of any of our product candidates for any indication. If we are unable to obtain regulatory approval for, and successfully commercialize, our product candidates, our business may be materially harmed and such failure may affect the viability of our other product candidates.
- Preclinical and clinical development is a lengthy, expensive and uncertain process. The results of preclinical studies and early clinical trials are not always predictive of future results. If our preclinical studies and clinical trials are not sufficient to support regulatory approval of any of our product candidates, we may incur additional costs or experience delays in completing, or ultimately be unable to complete, the development of such product candidate.
- Our product candidates are based on novel technologies, making it difficult to predict the timing, results and cost of product candidate development and likelihood of obtaining regulatory approval.
- We may encounter substantial delays in initiating or completing our clinical trials.
- Serious adverse events, undesirable side effects or other unexpected properties of our product candidates may be identified during development or after approval, which could lead to the discontinuation of our clinical development programs, clinical holds by regulatory authorities, refusal by regulatory authorities to approve our product candidates or, if discovered following marketing approval, revocation of marketing authorizations or limitations on the use of our product candidates thereby limiting the commercial potential of such product candidate.
- Interim, topline and preliminary data from our preclinical studies and clinical trials may change as more data become available and are subject to audit and verification procedures that could result in material changes in the final data.
- We rely on third parties to conduct, supervise and monitor our clinical trials and perform some of our research and preclinical studies. If these third parties do not satisfactorily carry out their contractual duties or fail to meet expected deadlines, our development programs may be delayed or subject to increased costs, each of which may have an adverse effect on our business and prospects.
- We face substantial competition, which may result in others discovering, developing or commercializing products more quickly or marketing them more successfully than us.
- We are currently party to several in-license agreements under which we acquired rights to use, develop, manufacture and/or commercialize certain of our platform technologies and resulting product candidates. If we breach our obligations under these agreements, we may be required to pay damages, lose our rights to these technologies or both, which would adversely affect our business and prospects.

- We are dependent on our license agreements and research and development agreements, or R&D Agreements, with various partners to develop and commercialize products using our technologies in various fields and indications as well as certain of our product candidates in certain geographies. The failure to maintain our R&D Agreements with our collaboration partners or the failure of our partners to perform their obligations under our R&D Agreements with them, could negatively impact our business.
- If we are unable to obtain and maintain sufficient intellectual property protection for our platform technologies and product candidates, or if the scope of the intellectual property protection is not sufficiently broad, our competitors could develop and commercialize products similar or identical to ours, and our ability to successfully commercialize our products may be adversely affected.

PART I

Item 1. Business

Business Overview

We are a clinical-stage biologics company focused on discovering and developing a novel class of engineered precision biologics, or EPBs, using our proprietary expanded genetic code technology platform that allows us to incorporate, in a site-specific manner, synthetic amino acids, or SAAs, into proteins within living cells. Our product candidates are designed to overcome the inherent limitations of conventional conjugation approaches that use natural amino acids for non-site-specific conjugation, offering potential safety and efficacy benefits to treat patients across multiple therapeutic areas. We believe that our technology allows us to engineer a single optimized structure by designing the conjugation chemistries, selecting the precise number of amino acids and conjugation positions in the protein, and expanding the types of payloads that can be conjugated. Our precision engineering capabilities and the broad applicability of our expanded genetic code technology platform have the potential to enhance and enable the therapeutic functions of conventional biologics and bio-conjugates.

Our SAA incorporation technology is designed to develop a wide array of product candidate modalities, such as antibody-drug conjugates, or ADCs, immuno-oncology conjugate, or IOC, bispecific antibodies, PEGylated peptides, modified cytokines and immuno-stimulating antibody conjugates, or ISACs. Our primary focus is on the ADC modality and two lead ADC product candidates in clinical development: ARX788 and ARX517. ARX788 is an anti-HER2 ADC currently being investigated in multiple clinical trials for the treatment of HER2-positive metastatic breast cancer and gastric cancer, and ARX517 is an anti-prostate-specific membrane antigen, or PSMA, ADC currently being investigated in an ongoing dose escalation Phase 1 clinical trial for the evaluation of the safety of ARX517 in the treatment of prostate cancer, including metastatic castration-resistant prostate cancer, or mCRPC.

On October 18, 2022, we announced a reprioritization of our product pipeline after conducting a strategic assessment that considered our cash runway and our product pipeline near term value creation opportunities, among other factors. As a result of our then-assessment, we paused the internal development of ARX788, as well as certain other programs, and, among other potential activities, decided to seek development partners to further its development outside of China.

During the first quarter of 2023, we decided to conduct a signal-finding study in the post-Enhertu metastatic breast cancer patient population. This decision was based, amongst other things, upon published data in China from ACE-Breast-01, preliminary data in the United States from ACE-Breast-03 and ACE-Pan-Tumor-01, which, in a small number of patients, showed anti-tumor activity in post-Enhertu (trastuzumab deruxtecan, or T-DXd), post-Kadcyla (ado-trastuzumab emtansine, or T-DM1) and HER2-low patients. Further, with the approval of Enhertu in the second line treatment setting, the third line treatment metastatic breast cancer landscape has changed, and given the clinical activity of ARX788 observed to date, we believe that there may be opportunity for ARX788 in the third line of HER2-positive metastatic breast cancer. This setting, as well as potentially additional opportunities for ARX788 should Enhertu be approved as a treatment for breast cancer in earlier lines of therapy, may represent a significant commercial opportunity. As such, we believe it is in our best interest to conduct a signal-finding study to determine if ARX788 has anti-tumor activity in the post-Enhertu patient population.

Additionally, ACE-Breast-02, the most advanced trial involving ARX788, demonstrated positive Phase 3 data in China, which further reinforced our decision to continue the internal development of ARX788, while redefining certain development characteristics. In light of these factors, we plan to conduct a signal-finding study that will include a 2:1 randomization of ARX788 versus standard of care in approximately 45 HER2-positive post-Enhertu metastatic breast cancer patients as an amendment to and under the previously paused Phase 2 ACE-Breast-03 study protocol.

As stated above, we are focusing our internal efforts on developing ARX788 and ARX517. Our most advanced product candidate, ARX788, is an anti-HER2 ADC currently being studied in breast, gastric and other solid tumor trials. The most advanced trial, ACE-Breast-02, is an ongoing Phase 3 clinical trial for HER2-positive metastatic breast cancer being conducted in China by our partner, NovoCodex Biopharmaceuticals Ltd., or NovoCodex, a subsidiary of Zhejiang Medicine Co. Ltd., or ZMC. In March 2023, we were informed by NovoCodex that this study has met its pre-specified interim primary efficacy endpoint with statistical significance, demonstrating a greater progression free survival, or PFS, benefit compared to the active control.

Our second most advanced ADC candidate, ARX517, is an anti-PSMA ADC currently being studied for the treatment of advanced prostate cancer. APEX-01 is an open-label Phase 1 clinical trial evaluating the safety and preliminary efficacy of ARX517 in the treatment of advanced prostate cancer, including mCRPC. Enrollment and dose escalation are ongoing, and we expect to report preliminary safety and efficacy data in the second half of 2023 at a major medical meeting and we are targeting the European Society for Medical Oncology, or ESMO, to do so. We believe that ARX517, if ultimately approved, has the potential to be a first-in-class ADC targeting PSMA.

Within our ADC franchise, while not our primary focus, we are also developing another earlier-stage product candidate, ARX305, an anti-CD70 ADC for the treatment of renal cell carcinoma, or RCC, and other cancers. The investigational new drug application, or IND, for ARX305 received U.S. Food and Drug Administration, or FDA, clearance in February 2022. NovoCodex is our commercial and development partner in China for ARX305, where we may use data generated by NovoCodex to support our clinical development and regulatory filings. See “*Business Overview—Collaborations—License Agreement with NovoCodex (ARX788)*” for more information on our agreement with NovoCodex, including our rights to use such data. NovoCodex initiated the Phase 1 trial for ARX305 in the second half of 2022, and depending on the data from NovoCodex’s Phase 1 study, as stated above, we may seek to initiate our own Phase 1 clinical trial. NovoCodex is the main sponsor of Phase 1 development of ARX305, and we will be reimbursed for our own internal development costs, up to a certain amount.

Additionally, our IOC franchise consists of product candidates targeting broad immuno-oncology applications. These candidates include ARX102, a smart PEG-IL-2cytokine. We are currently conducting pre-clinical IND-enabling studies for ARX102, and our partner, Sino Biopharmaceutical Limited, or Sino Biopharma, has submitted their IND for ARX102 to the China National Medical Products Administration, or NMPA. As with NovoCodex and ARX305, we may draw from this external trial to potentially inform our own clinical trials.

In connection with our pipeline programs and platform technologies, we own or control over 800 issued patents and pending patent applications.

The following charts summarize our current internal and external product candidate pipelines, respectively.

Internal Product Pipeline

Candidate	Indications	Trial Setting (Name)	Preclinical	Phase 1	Phase 2	Phase 3
LEAD PRODUCT CANDIDATES						
ADC Oncology						
ARX788 Anti-HER2 ADC	HER2+ mBC <i>(FDA granted Fast Track designation)</i>	Post-T-DXd/T-DM1/Tucatinib (ACE-Breast-03) (enrollment closed)	Ambrx Sponsored U.S. Study			
	HER2+ Stage 2/3 BC	Neoadjuvant Monotherapy (I-SPY 2.2)	Ambrx Supported U.S. Consortium Study			
	Solid Tumors	ACE-Pan-Tumor-01 (enrollment closed)	Ambrx U.S./Australia Study with cohorts for gastric cancer and HER2 low BC			
ARX517 Anti-PSMA ADC	PSMA	PSMA (APEX-01)	Ambrx Sponsored U.S. Study			
SECONDARY PRODUCT CANDIDATES						
ADC Oncology						
ARX305 Anti-CD70 ADC	Cancer	RCC and other cancers	Ambrx Sponsored			
Immuno-Oncology						
ARX102 Smart PEG-IL 2	Cancer	—	Ambrx Sponsored			

External Product Pipeline

Candidate	Indications	Trial Setting (Name)	Preclinical	Phase 1	Phase 2	Phase 3
ADC Oncology						
ARX788 Anti-HER2 ADC	HER2+ mBC	2L+ (ACE-Breast-01)	NovoCodex Sponsored			
		2L+ (ACE-Breast-02)	NovoCodex Sponsored			
	HER2+ Advanced BC	ACE-Breast-08	NovoCodex Sponsored			
	HER2+ Gastric Cancer	ACE-Gastric-02	NovoCodex Sponsored			
ARX305 Anti-CD70 ADC	Cancer	RCC and other cancers	NovoCodex Sponsored			
Immuno-Oncology						
ARX102 Smart PEG-IL 2	Cancer	—	Sino Biopharma Sponsored			

Product Pipeline Milestones and Progression

Our current focus is to discover and develop a pipeline of ADCs, to treat a broad range of diseases and disorders, with an initial focus on cancers with a high unmet medical need. We believe that combining our pioneering efforts in expanded genetic code and site-specific bio-conjugates with a team of dedicated professionals bound by a culture and vision that embraces innovation, practicality, and accountability will allow us to pursue our goals.

ARX788:

ACE-Breast-01 is an ongoing Phase 1 clinical trial of ARX788 which is being conducted in China by NovoCodex in HER2-positive metastatic breast cancer patients whose diseases have failed other available therapies, including anti-HER2 ADCs. As previously reported, in this trial, we have observed promising anti-tumor activity with a confirmed objective response rate, or ORR, of 66% (19 of 29 patients) in the cohort of patients receiving 1.5 mg/kg of ARX 788 at every three weeks (Q3W) as of December 14, 2021. In the cohorts of patients receiving 1.3 mg/kg of ARX788 at Q3W or every four weeks (Q4W), we have observed an ORR of 50% (8 of 16 patients). Safety and efficacy data from ACE-Breast-01 was presented at the 2021 San Antonio Breast Cancer Symposium 2021, or SABCS, and is published in Clinical Cancer Research ((2022) 28 (19): 4212–4221 (Zhang, et al.).

ACE-Breast-02 is a large ongoing randomized, controlled pivotal Phase 3 clinical trial of ARX788 investigating ARX788 in the treatment of HER2-positive patients with locally advanced or metastatic breast cancers in China being conducted by NovoCodex. Enrollment in this study has completed, and results from an interim analysis have been positive, as the study met its pre-specified interim primary efficacy endpoint with statistical significance, demonstrating a greater PFS benefit compared to the control. Based on these results, NovoCodex plans to submit a communication application to seek marketing approval in China, pending discussion with the NMPA.

ACE-Breast-03 is an ongoing Phase 2 multi-center clinical trial evaluating ARX788 for patients whose metastatic disease is resistant or refractory to T-DXd, T-DM1, or tucatinib-containing regimens. Preliminary data was presented during a Spotlight Poster Presentation at SABCS 2022 pertaining to post- Kadcyla HER2-positive metastatic breast cancer patients. The preliminary results presented at the SABCS demonstrated encouraging response rates and safety results, particularly given the significant medical need for new therapies among patients whose disease continues to progress after receiving multiple lines of therapy. None of the patients experienced drug-related serious adverse events, or SAEs, and all adverse events, or AEs, were well tolerated with no treatment discontinuations from AEs. As part of our strategic reprioritization announced in October 2022, enrollment for the trial was paused; however, patients that were already enrolled are still being treated. As described above we plan to amend the previously paused Phase 2 ACE-Breast-03 study protocol to include a signal-finding study that will include a 2:1 randomization of ARX788 versus standard of care in approximately 45 HER2-positive post-Enhertu metastatic breast cancer patients, while redefining certain of the development characteristics.

ACE-Gastric-01 is a Phase 1 clinical trial of ARX788 in HER2-positive metastatic gastric/gastroesophageal junction adenocarcinoma, or GEJ, cancer where patients have failed other available therapies, including Herceptin (trastuzumab), which was being conducted in China by our partner NovoCodex. In this trial, we believe encouraging anti-tumor activity was observed in the cohorts of patients receiving 1.7 mg/kg of ARX788 Q3W with a 43% (3 of 7) confirmed ORR, 1.5 mg/kg of ARX788 Q3W with a 46% (6 of 13 patients) confirmed ORR, and a 43% (3 of 7 patients) confirmed ORR in the cohort of patients receiving 1.3 mg/kg of ARX788 at Q3W as of December 14, 2021.

ACE-Pan-Tumor-01 is an ongoing Phase 1 dose escalation and expansion trial in the United States and Australia for patients with various tumors with HER2 expression, including advance HER2-positive and HER2-low expressing breast cancer. As part of our strategic reprioritization announced in October 2022, enrollment for this trial was paused; however, patients that were already enrolled are still being treated.

In 2022, ARX788 was selected to participate in I-SPY 2.2, an internationally renowned Phase 2 clinical trial assessing developing targeted agents to combine them with less toxic chemotherapeutic regimens or to completely replace cytotoxic chemotherapy. I-SPY 2.2 is a two-arm study, investigating candidates both as monotherapies and in combination with other agents. ARX788 is currently being assessed as a single agent in patients with HER2-positive early-stage breast cancer in the neoadjuvant setting under the ongoing I-SPY 2.2 clinical trial.

We expect to have a preliminary clinical data update regarding ACE-Pan-Tumor-01 and ACE-Breast-03 in late 2023 and 2024, respectively.

Additionally, although we have not been required to repeat Phase 1 trials to initiate Phase 2 or Phase 3 HER2-positive metastatic breast cancer trials in the United States, the FDA or comparable foreign regulatory authorities may not interpret the results of the trials being conducted in China by our partner, NovoCodex as we do, and may require additional trials.

As stated above, in addition to external development, our clinical strategy involves additional ongoing clinical trials, including the amendment to ACE-Breast-03 protocol discussed above, ACE-Pan-Tumor-01, and I-SPY 2.2.

FDA and NMPA Recognition of ARX788:

We received Fast Track designation from the FDA for ARX788 as a monotherapy for the treatment of HER2-positive metastatic breast cancer patients who have received one or more prior anti-HER2-based regimens in the metastatic setting. In addition, the NMPA granted ARX788 Breakthrough Therapy designation for the second-line treatment of HER2-positive metastatic breast cancer in May 2021, which was one of only five product candidates that were granted Breakthrough Therapy designations by the NMPA in 2021.

We received Orphan Drug designation from the FDA for the treatment of gastric cancer, including cancer at the GEJ.

ARX517:

APEX-01 is an ongoing Phase 1, first-in-human, open label dose escalation and dose expansion clinical trial investigating the safety and preliminary efficacy of ARX517, an ADC targeting PSMA, in patients with advanced prostate cancer whose tumors have progressed on at least two prior FDA-approved treatments. Initial preliminary data was reported in February 2023 and showed a prostate-specific antigen, or PSA, decrease of greater than 50% in PSA levels from baseline in the first three patients with metastatic prostate cancer receiving ARX517 at 2.0 mg/kg (Cohort 6). Two of these patients experienced a greater than 90% decline in PSA levels, and one patient with soft tissue measurable disease experiencing a RECIST v1.1 partial response. A PSA reduction of 30% or more was observed in one or more patients in all previous cohorts starting at 0.64 mg/kg. Patients were heavily pre-treated, with a median of five prior lines of therapy, including Pluvicto. No drug-related SAEs or dose limiting toxicities, or DLTs, had been observed. Patients were not screened to determine the presence of PSMA antigen.

In addition to our own clinical development plans, we may leverage existing partnership relationships, as well as potentially develop new ones, in order to facilitate the progression of our product candidates.

Conventional Biologics, ADCs and Bio-Conjugates, and Their Inherent Limitations

Biologics have been used increasingly on a global basis and in multiple therapeutic areas, expanding the overall drug market and reducing the market share of small molecule drugs. The market for biologics initially included conventional biologics such as insulin, growth hormones, and monoclonal antibodies. However, despite the clinical benefit provided by these natural peptides and antibodies, there remained a significant medical need for more effective therapies. Since then, the industry has developed bio-conjugates and ADCs to generate more efficacious treatments, including approved drugs such as Enhertu, Kadcyla, Adcetris (brentuximab vedotin) and Trodelvy (sacituzumab govitecan-hziy).

Bio-conjugates are the product of joining two or more biologically active components into a single drug. These constructs can introduce new mechanisms of action, increase efficacy, reduce toxicity and provide improved clinical outcomes and convenience. Bio-conjugates have also significantly expanded the potential landscape of targets that can be accessed by conventional biologics by providing several new approaches for each target, such as an ADC or an ISAC.

Today's leading bio-conjugates typically rely on cysteine and lysine, two naturally occurring amino acids with "handles" for conjugations. Unfortunately, utilizing natural amino acids for conjugation can limit drug design in several ways. First, the conjugation chemistry is predetermined with limited room to optimize reactivity, stability and selectivity. Second, the location and number of these natural amino acids within the protein further diminish the ability to control the site of conjugation and the number of conjugations. Third, additional manufacturing steps and controls are required for conventional conjugations. As such, conventional conjugation techniques result in a mixture of random, non-uniform and un-optimized drug conjugates that can potentially limit therapeutic efficacy and introduce drug safety concerns.

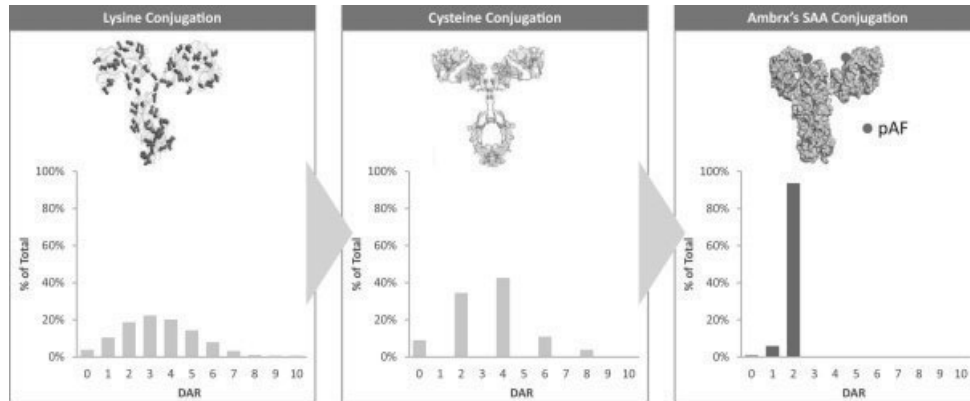
Designing the conjugation chemistry and selecting the precise number and conjugation positions in the protein are critical elements to *in vivo* stability, offering potential safety and efficacy benefits. We believe that conjugation chemistry using natural amino acids is more likely to result in the toxic payload detaching from the antibody before reaching the tumor, a leading cause for off-target toxicity. The random placement of conjugates and unstable chemical bonds has further hampered the safety and efficacy of conventional bio-conjugates. For example, an antibody can have up to 80 lysine residues available for conjugation and attempting to conjugate a specific number of payload molecules to every antibody molecule, which is referred to as the drug-to-antibody ratio, or DAR, cannot be achieved homogeneously due to the random nature of the reaction of conventional approaches. Given these limitations, conventional conjugation methods target average DAR, rather than a homogeneous DAR where each antibody has the same number of drug conjugations. As a result, a substantial amount of the antibodies in the mixture will not have the same DAR as the average DAR, with some antibodies remaining "naked" with no drug attached, while others become "under- or over-populated" with attached linker-payloads. This heterogeneous population of drug-loaded antibodies can impact properties such as drug clearance, pharmacokinetics, or PK, and biodistribution. As such, drug manufacturers must strive to minimize the standard deviation of the DAR from the stated average DAR in order to prevent undesirable or unpredictable drug properties, including dosing challenges and safety issues.

Our Solution

Our product candidates are designed to overcome the inherent limitations of these conventional conjugation approaches, offering potential safety and efficacy benefits to treat patients across multiple therapeutic areas. Key elements of our approach to developing a novel class of EPBs include:

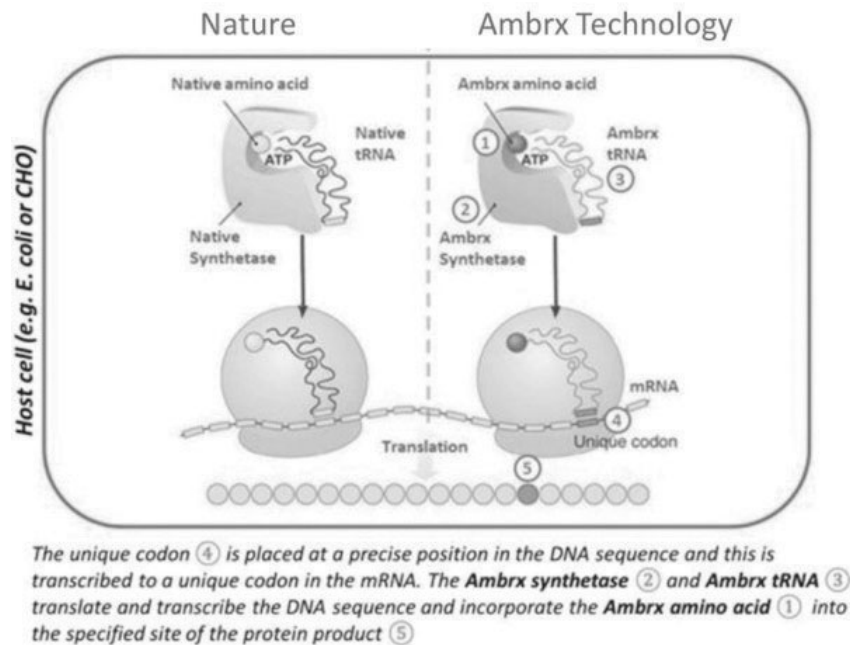
- Our proprietary expanded genetic code technology platform allows us to incorporate SAAs in a site-specific manner into proteins within living cells, including both bacterial and mammalian cells.
- The site-specifically incorporated SAA creates a unique and predictable attachment point for our conjugations, allowing us to obtain over 90% homogeneity.
- We have a wide range of proprietary payloads and linkers for site-specific conjugation to achieve the designed biological functions for our EPBs.

Our platform allows for highly predictable properties, including consistent homogeneity and stability, which translates into potential expansion of the therapeutic window compared to conventional approaches. The figure below summarizes DAR, in the case of an ADC, for both conventional technologies that use natural amino acids, such as lysine to cysteine with an average DAR of approximately four, and our proprietary conjugation technology, which uses SAAs for conjugation. To achieve effective homogeneity, we have created site-specific ADCs with payloads conjugated onto the incorporated SAA, with more than 90% achieving DAR 2 and the rest achieving DAR 1.



Expanded Genetic Code and Site-Specific SAAs

Our proprietary expanded genetic code technology platform allows us to site-specifically incorporate SAAs into proteins within living cells. It provides a fundamentally original approach to expressing a new class of proteins in living cells. Our approach is described in the figure below.



The components of this process are:

- (1) **Our SAAs:** We use SAAs with unique chemical handles not found on naturally occurring amino acids, which serve as unique and predictable attachment points for our conjugations. SAAs provide us with freedom in designing our conjugation chemistry to incorporate desired specificity and stability unmatched when using natural amino acids.
- (2) **Our orthogonal tRNA synthetase:** Our specially engineered tRNA synthetase is an enzyme that is imported into the cell to catalyze a reaction that loads only a specific SAA onto our orthogonal tRNA (transferring RNA). Our orthogonal tRNA synthetase will not recognize any of the 20 natural amino acids and will not load the recognized specific SAA onto any native tRNAs in the employed cell system.
- (3) **Our orthogonal transferring RNA, or tRNA:** Our specially engineered RNA molecule is responsible for transferring the loaded amino acid by its corresponding tRNA synthetase to the ribosome, which is the protein factory of a cell. There, the amino acids are assembled into a protein following the sequence instruction of messenger RNA, or mRNA, transcribed from the DNA of the gene of interest. Our orthogonal tRNA is imported into the cell and cannot be recognized by any native tRNA synthetases in the cell. It can only be recognized by our imported orthogonal tRNA synthetase and loaded with the specific SAA corresponding to the orthogonal tRNA synthetase.
- (4) **Our unique codon:** In nature, all proteins consist of 20 natural amino acids, with each acid encoded at the DNA level by a set of triplet codons. The linear orders of these amino acids are determined by the sequence of DNA of each gene. Our technology platform expands this fixed genetic code to code an SAA, for example by enabling a specific stop codon, such as an amber stop codon, which does not code any natural amino acids.
- (5) **Our precision engineered protein incorporated with site-specific SAA:** When we incorporate an SAA into a protein, we mutate the codon at a desired site into the amber stop codon in the DNA of the gene of interest, to provide instructions to the cell machinery to incorporate the SAA. The DNA of the gene of interest, orthogonal tRNA and orthogonal tRNA synthetase are transferred into the cell system, and, in the case of mammalian systems, transferred into the genome of the cell. The DNA is transcribed into mRNA for the gene of interest, tRNA and mRNA of orthogonal tRNA synthetase which is further translated into the orthogonal tRNA synthetase enzyme. Into the cell culture medium, we feed the cell with an SAA. The SAA is recognized by our imported enzyme, orthogonal tRNA synthetase, and is loaded onto the imported orthogonal tRNA. Our orthogonal tRNA transfers the loaded SAA to the protein assembling factory, the ribosome, where the 20 natural amino acids as well as our SAA are assembled linearly by following the strict instruction of the mRNA for the gene of interest, such as an antibody. When the amber stop codon is reached, instead of terminating the protein synthesis as would naturally occur, this codon is recognized by our engineered orthogonal tRNA. Upon recognition, the SAA that is loaded on the tRNA is now incorporated into this pre-identified location. Using this process, protein synthesis continues until the entire desired protein is synthesized. We have developed systems to incorporate SAAs into proteins in industry standard cell lines, including *E.coli* and Chinese hamster ovarian, or CHO, cells.

Our Protein Expression Systems: EuCODE and ReCODE

EuCODE and ReCODE are the core platforms that allow us to incorporate SAAs into proteins in mammalian and bacterial cells, respectively. The concept and components for this technology were first developed at The Scripps Research Institute, or TSRI, and were exclusively licensed to us in 2003. We improved the bacterial incorporation technology developed at TSRI to establish our ReCODE platform. Our ReCODE system can be utilized for the expression of small, single domain and simple proteins that do not require post-translational modification. We subsequently invented a more advanced platform, EuCODE, which is a mammalian expression system for large, multi-domain and more complex proteins. EuCODE can also provide post-translational modifications, such as glycosylation, which are critical for certain functions of biologics. We use our EuCODE and ReCODE expression platforms in the manufacturing of our product candidates in various stages of clinical development.

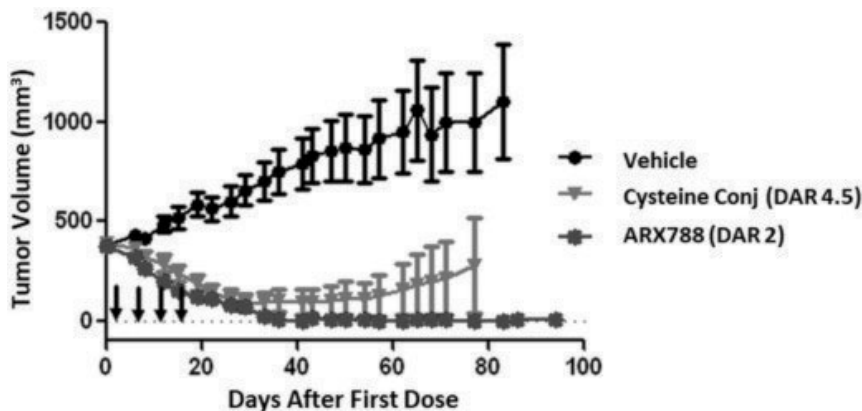
Our Site-Specific Conjugation Technologies

After the proteins are made by our EuCODE and ReCODE technologies, we conjugate a designed moiety, such as PEG or payload to the SAAs, to achieve a desired therapeutic effect. We have a portfolio of designed SAAs with unique chemical handles for site-specific conjugation.

Taking SAA para-acetylphenylalanine, or pAF, as an example, the ketone functional group on pAF is designed to form an oxime bond specifically with its counterpart hydroxylamine group. When creating an ADC, such as ARX788 or ARX517, after the site-specific incorporation of pAF into the antibody, the ketone group is presented to the specific location on the antibody and is ready for conjugation. Under appropriate conditions, upon mixing the antibody incorporated with pAF and AS269, which is designed to include a hydroxylamine group, the ketone group of pAF on the protein will react specifically with hydroxylamine group on AS269 to form an oxime bond. As a result, AS269 is conjugated site-specifically to the location where pAF is incorporated into the antibody, yielding a homogeneous ADC.

The oxime bond formed on our protein has been demonstrated to be highly stable under physiological conditions. Through multiple preclinical studies and clinical trials conducted by us, cleavage of the bond has not been detected, even after the conjugated proteins were degraded into single amino acids. In the case of ARX788, the detectable metabolite was pAF-AS269, in which AS269 remained conjugated to pAF through the oxime bond, demonstrating the stability of the chemical bond.

In preclinical HER2-positive xenograft models, anti-tumor activity of ARX788 was tested against an ADC which was produced using conventional cysteine conjugation. ARX788 uses our proprietary AS269 payload conjugated with oxime chemistry, while the conventional ADC was conjugated using maleimide chemistry. As depicted in the graphic below, we observed that our site-specific conjugation resulted in improved anti-tumor activity, even at a lower DAR of 2, compared to the conventional ADC, which has a DAR of 4.5.



We believe the enhanced anti-tumor activity versus conventional ADCs demonstrated by ARX788 is a result of improved ADC stability and can be translated into more efficient and targeted delivery of the payload to the tumor.

Our Proprietary Payloads and Linkers for Conjugation

When coupled with the flexible nature of our bio-conjugation chemistry, our portfolio of proprietary payloads and linkers enable us to optimize potential product candidates in the design phase by testing and selecting those with the best features.

Our collection of proprietary cytotoxic payloads, which include tubulin inhibitors and DNA alkylating agents, can be coupled with a wide selection of proprietary linkers, both cleavable and non-cleavable, to meet various design needs. As an example, AS269 is specifically designed to form a highly stable covalent bond with our synthetic amino acids and to kill tumor cells only upon entry into the cell when aided by the conjugated targeting antibody, thereby reducing off-target concerns. In multiple cell-based assays and animal models of cancer, we observed broad activity for AS269, making it an attractive candidate to use in our current and potential future bio-conjugates. AS269 is generally non-cell permeable and appears to be a poor substrate for multidrug resistance proteins, or MDRs, which could enhance its potency and reduce cancer cell resistance. In preclinical studies for all of our current ADC programs, including ARX788, ARX517 and ARX305, we observed that ADCs designed in conjunction with AS269 outperformed other ADC designs. Given the promising preclinical data, we advanced three ADC programs using the AS269 payload and this payload has the potential to provide not only safety and efficacy benefits, but also a streamlined manufacturing process with a single payload drug master file.

Beyond cytotoxic payloads used for our ADC product candidates, we have a portfolio of proprietary PEGs, small molecule targeting agents, potent TLR7/8 agonists and other components for designing EPBs. We continue to explore novel approaches, including payloads that enable different mechanisms of action, prodrug strategies and conditional activation technology.

Our Innovation Engine

We believe that our expanded genetic code technology platform, which provides us with the ability to incorporate, in a site-specific manner, SAAs into proteins within living cells, is a fundamental breakthrough in drug design. We believe our proprietary platform will serve as an innovation engine and we can leverage our EPBs to take recombinant DNA technologies into new territories by improving and enabling the field of bio-conjugates. We intend not only to advance our current programs through clinical development but also to design and develop additional EPBs.

Our proprietary and enabling technology includes algorithms to scan and select promising sites for protein modification that preserve the native structure and function of proteins, antibodies, and antibody fragments, while enhancing their performance as bio-conjugates. We optimize EPBs by rapidly screening a panel of homogeneous recombinant proteins with SAAs inserted at predefined locations. This screening includes parameters such as expression, conjugation efficiency, and solubility, and a range of other biophysical properties as well as *in vitro* and *in vivo* biological characteristics such as pharmacology, potency and toxicity.

Our ability to rapidly assess and optimize bio-conjugates based on how different structures and payloads interact to enhance therapeutic performance is an invaluable design process typically reserved for modern small molecule drugs. As a result, we can create and test multiple conjugation structures in the design phase, generating data in cell-based and animal-based models of disease before selecting development candidates to advance into further testing and clinical trials.

As the pioneer and a leader in the EPB field, we continue to invest in the innovation and expansion of our underlying technology platforms, EuCODE and ReCODE. We plan to explore additional capabilities, including (i) incorporating more SAAs into proteins, thereby allowing more chemistries and functionalities, (ii) developing design systems that may allow us to incorporate two distinct SAAs into one protein, and (iii) further engineering our cell lines and expanding our approach into more cellular systems.

We believe our proprietary conjugation technologies provide us with a unique advantage compared to other bio-conjugate companies, which could allow us to continue advancing and expanding our pipeline across our core ADC and IOC franchises.

Summary of Our Product Pipeline

We have engineered a pipeline of ADC product candidates that are diversified across mechanisms of action, target indications and development stages. We believe our platform and technologies can significantly improve patients' treatment outcomes in indications of high unmet medical need. Our focus is to discover, develop and commercialize EPBs, both internally and through partnerships with other companies worldwide, with new and improved properties to treat and potentially cure a broad range of cancers. The following charts summarize our current internal and external product candidate pipelines, respectively.

Internal Product Pipeline

Candidate	Indications	Trial Setting (Name)	Preclinical	Phase 1	Phase 2	Phase 3
LEAD PRODUCT CANDIDATES						
ADC Oncology						
ARX788 Anti-HER2 ADC	HER2+ mBC <i>(FDA granted Fast Track designation)</i>	Post-T-DXd/T-DM1/Tucatinib (ACE-Breast-03) (enrollment closed)	Ambrx Sponsored U.S. Study			
	HER2+ Stage 2/3 BC	Neoadjuvant Monotherapy (I-SPY 2.2)	Ambrx Supported U.S. Consortium Study			
	Solid Tumors	ACE-Pan-Tumor-01 (enrollment closed)	Ambrx U.S./Australia Study with cohorts for gastric cancer and HER2 low BC			
ARX517 Anti-PSMA ADC	PSMA	PSMA (APEX-01)	Ambrx Sponsored U.S. Study			
SECONDARY PRODUCT CANDIDATES						
ADC Oncology						
ARX305 Anti-CD70 ADC	Cancer	RCC and other cancers	Ambrx Sponsored			
Immuno-Oncology						
ARX102 Smart PEG-IL 2	Cancer	—	Ambrx Sponsored			

External Product Pipeline

Candidate	Indications	Trial Setting (Name)	Preclinical	Phase 1	Phase 2	Phase 3
ADC Oncology						
ARX788 Anti-HER2 ADC	HER2+ mBC	2L+ (ACE-Breast-01)	NovoCodex Sponsored			
		2L+ (ACE-Breast-02)	NovoCodex Sponsored			
	HER2+ Advanced BC	ACE-Breast-08	NovoCodex Sponsored			
	HER2+ Gastric Cancer	ACE-Gastric-02	NovoCodex Sponsored			
ARX305 Anti-CD70 ADC	Cancer	RCC and other cancers	NovoCodex Sponsored			
Immuno-Oncology						
ARX102 Smart PEG-IL 2	Cancer	—	Sino Biopharma Sponsored			

ADC Franchise

Conventional ADCs can have significant limitations in conjugation chemistry, conjugation position and homogeneity, which may limit their therapeutic potential and give rise to safety concerns. We have designed the product candidates in our ADC franchise with the potential to effectively and safely deliver a cytotoxic payload to a tumor site, benefiting from characteristics generally not available to conventional ADCs such as increased stability of conjugation chemistries, optimized conjugation locations and improved homogeneity.

Our focus in our ADC program is on ARX517, an anti-PSMA ADC currently being studied in prostate cancer, particularly mCRPC, and ARX788, an anti-HER2 ADC currently being studied broadly in breast and gastric cancer, including cancer at the GEJ, and other solid tumors. ARX517 is currently being investigated in an ongoing Phase 1 trial for prostate cancer. The most advanced trial of ARX788 is an ongoing Phase 3 trial for HER2-positive metastatic breast cancer in China, ACE-Breast-02, and we have multiple additional potentially registrational global trials ongoing, such as ACE-Gastric-02 and ACE-Breast-08. ARX788 was also selected to participate in I-SPY 2.2, an adaptive trial investigating new agents combined with standard therapy in patients with Stage II and III breast cancer, in the neoadjuvant setting.

In addition to ARX788 and ARX517, our internal ADC franchise has one additional program, ARX305, an anti-CD70 ADC for CD70-positive RCC and other cancers. The IND application for ARX305 received clearance from the FDA, and we may initiate a Phase 1a clinical trial, pending other considerations, including data gathered by NovoCodex, our development partner with respect to ARX305. ARX517 and ARX305 use the same cytotoxic payload as ARX788, which we believe may streamline development, clinical, regulatory, and manufacturing requirements.

ARX517 (PSMA ADC)

ARX517 targets the PSMA expressed on prostate cancer cells. PSMA is a clinically important biomarker of prostate cancer which is highly over-expressed in mCRPC. PSMA is also widely expressed in the neovasculature of other solid tumors, such as pancreatic, non-small-cell lung cancer, or NSCLC, and ovarian, making it an attractive target for ARX517. We received IND clearance for ARX517 from the FDA in October 2020.

Prostate cancer represents a significant unmet medical need and sizable market opportunity. There were 1.4 million new cases of prostate cancer and 375,000 associated deaths worldwide in 2020 while the American Cancer Society estimates the number of new U.S. prostate cancer diagnoses in 2023 will reach 288,300, with 34,700 deaths. Based on U.S. data, the five-year survival rate is greater than 95% overall, but only 32.3% for patients diagnosed with distant metastases. For men, prostate cancer is the second most frequent cancer and the fifth leading cause of cancer death. The global market for prostate cancer therapies was estimated to be \$9.3 billion in 2018 and is forecast to grow to \$12.8 billion by 2028. In March 2022, Pluvicto, a 177 Lutetium radioligand targeting PSMA, was approved by the FDA for the treatment of adult patients with PSMA-positive mCRPC who have been treated with androgen receptor, or AR, pathway inhibition and taxane-based chemotherapy. We believe this approval corroborates the clinical relevance of the PSMA target in mCRPC. We believe that the data generated in our preclinical studies, including studies comparing ARX517 to the standard of care therapies in *in vivo* tumor models, demonstrates the ability of our ADCs to provide a different mechanism of action and potential benefits over existing therapies.

ARX788

ARX788, is an anti-HER2 ADC. ARX788 is in ongoing Phase 2/3 trials for HER2-positive metastatic breast cancer and gastric/GEJ cancer to support potential registration in China. In an ongoing Phase 1 clinical trial of ARX788 in HER2-positive breast cancer in China, or ACE-Breast-01, as of December 14, 2021, in the 1.5 mg/kg Q3W cohort, ARX788 had achieved a confirmed ORR of 66% (19 of 29 patients) and a DCR of 100%, and a confirmed ORR of 50% (8 of 16 patients) and DCR of 88% in the 1.3 mg/kg cohorts. As previously reported, ARX788 has also shown a favorable tolerability profile in this trial, with few drug-related SAEs reported, in heavily pre-treated cancer patients whose disease had failed other available therapies, including currently approved and experimental HER2-targeting therapies, such as ADCs, TKIs and bispecific antibodies.

The FDA granted ARX788 Fast Track designation as monotherapy for the treatment of advanced or metastatic HER2-positive breast cancer patients who have received one or more prior anti-HER2-based regimens in the metastatic setting and Orphan Drug designation for the treatment of gastric cancer, including cancer at the GEJ, in December 2020 and January 2021, respectively. The NMPA granted ARX788 Breakthrough Therapy designation for the second-line treatment of HER2-positive metastatic breast cancer in May 2021.

As stated above, results from an interim analysis of ACE-Breast-02, ongoing randomized, controlled pivotal Phase 3 clinical trial of ARX788 investigating ARX788 in the treatment of HER2-positive patients with locally advanced or metastatic breast cancers in China, have been positive, as the study met its pre-specified interim primary efficacy endpoint with statistical significance, demonstrating a greater PFS benefit compared to the control. Based on these results, NovoCodex plans to submit a communication application to seek marketing approval in China pending discussion with the NMPA.

ARX788 is a homogeneous and highly stable ADC, which targets the HER2 receptor and contains two cytotoxic AS269 payloads site-specifically conjugated to a trastuzumab-based antibody. ARX788 was designed to maximize its potential for anti-tumor activity by optimizing the number and position of the payloads and the chemical bonds that conjugate the payloads to the antibody. AS269 is a proprietary payload specifically designed to form a highly stable covalent bond with our SAAs and kill tumor cells only upon entry into the cell when aided by the conjugated targeting antibody, thereby limiting off-target effects on healthy tissue.

We believe ARX788 has the potential to significantly improve outcomes for HER2-positive cancers, including those in patients with metastatic disease and in earlier stages of adjuvant and neoadjuvant settings. Our initial focus is on the treatment of patients with HER2-positive breast and gastric cancers, including at the GEJ. However, we believe ARX788 may benefit a broader spectrum of cancer patients, including HER2-low breast cancer patients, as well as HER2-positive and HER2-low patients in other malignancies, such as non-small cell lung cancer, or NSCLC, urothelial, biliary tract, colon, ovarian and pancreatic cancers. We may seek new partnerships with companies outside of China to initiate multiple trials to expand indications and geographic reach. Dosing is ongoing by both us and NovoCodex across several clinical trials.

Adhering to our clinical strategy, we and our partner NovoCodex are currently conducting and/or analyzing data from the following ARX788 clinical trials globally (ex-China) and in China, respectively:

- ACE-Breast-01 (NovoCodex): Phase 1 dose escalation and cohort expansion clinical trial in China for patients with HER2-positive advanced or metastatic breast cancer whose diseases have failed multiple prior lines of therapy.
- ACE-Breast-02 (NovoCodex): Phase 3 randomized clinical trial in China for HER2-positive advanced or metastatic breast cancer patients who have previously received first-line treatment of trastuzumab and less than two lines of chemotherapy.
- ACE-Breast-03 (Ambrx): Phase 2 single-arm clinical trial in the United States for HER2-positive metastatic breast cancer patients whose diseases have failed T-DM1 and/or T-DXd, and/or tucatinib-containing regimens. Enrollment for this trial has been paused, but patients already enrolled are still being treated. We plan to amend the protocol under the study to conduct a signal-finding study that will include a 2:1 randomization of ARX788 versus standard of care in approximately 45 HER2-positive

post-Enhertu metastatic breast cancer patients, while redefining certain of the development characteristics.

- ACE-Breast-08 (NovoCodex): Phase 1b/2 single arm clinical trial in China for HER2-positive breast cancer patients who have failed prior Herceptin and TKI treatment.
- ACE-Pan-Tumor-01 (Ambrx): Phase 1 dose escalation and expansion clinical trial in the United States and Australia for patients with various tumors with HER2 expression. Enrollment for this trial has been paused, but patients already enrolled are still being treated.
- ACE-Gastric-02 (NovoCodex): Phase 2/3 randomized clinical trial initially in China for patients with HER2-positive gastric/GEJ cancer.

In addition, the following ARX788 investigator-sponsored clinical trials are ongoing/planned:

- ACE-Breast-06 (NovoCodex): An ongoing Phase 2 single arm clinical trial in China for advanced HER2-positive metastatic breast cancer.
- ACE-Breast-07 (NovoCodex): An ongoing Phase 2 single arm clinical trial in China in HER2-low breast cancer.
- DREAM-02 (NovoCodex): An ongoing Phase 2 single arm clinical trial in China of pyrotinib maleate combined with ARX788 as neoadjuvant therapy in the treatment of HER2-positive stage II-III breast cancer.
- I-SPY 2.2 (Ambrx): An ongoing Phase 2 clinical trial in the United States sponsored by Quantum Leap Healthcare Collaborative for HER2-positive breast cancer patients in the neoadjuvant setting for ARX788 as single agent.
- ACE-Combo-02 (NovoCodex): A planned Phase 1 clinical trial in China evaluating ARX788 combined with toripalimab in patients with HER2-expressing or mutated advanced solid tumors.

In June 2013, we entered into a collaboration and license agreement with ZMC, which was subsequently transferred to NovoCodex, pursuant to which NovoCodex is responsible for all development and commercialization activities related to ARX788 in China. We are entitled to receive tiered royalties as high as mid-teens range on aggregate net sales of ARX788 in China, while NovoCodex is entitled to receive low single-digit royalties on sales outside of China.

On October 18, 2022, we announced a reprioritization of our product pipeline after conducting a strategic assessment that considered our cash runway and our product pipeline's near term value creation opportunities, among other factors. As a result of our assessment, we paused the internal development of ARX788. However, due to the factors described above, we have determined it is in our best interest to continue with the internal development of ARX788.

Approximately one woman in eight will be diagnosed with invasive breast cancer in her lifetime. In 2023, it is estimated that 300,000 new U.S. cases of invasive breast cancer will be diagnosed in women, 44,000 of whom are estimated to die from breast cancer. Although breast cancer has an overall five-year survival rate of 90%, the rate is just 30% for those diagnosed with distant metastases, based on U.S. data. One in 39 of these women is expected to die of this disease. The market for HER2 expressing breast cancer is estimated to exceed \$9 billion in 2022. With the advent of new HER2-targeting agents and next-generation HER2 ADCs, the market is forecasted to grow to over \$16 billion by the end of this decade. Part of this growth is anticipated to come from a newly created segment of breast cancer: HER2-low expressers (IHC 0 or 1 or IHC 2+, FISH 0, following the recent additional approval of Enhertu, the first next-generation HER2 ADC for HER2-low expressers in August 2022). The prevalence of HER2-low expression is significant: approximately 50% of all breast cancer patients. While gastric cancer has a lower incidence rate of approximately one in 95 for men and one in 154 for women in the United States, its five-year survival rate, overall, is significantly lower at 33%, and just 6% for those diagnosed with distant metastases. In addition to the market for HER2-expressing breast and gastric cancer therapeutics, other HER2-expressing cancers such as NSCLC, ovarian, urothelial, colon, biliary tract and pancreatic cancers represent additional market opportunities.

ARX305 (CD70 ADC)

ARX305 targets the CD70 receptor on cancer cells. CD70 is over-expressed in a broad range of solid and hematologic tumors such as RCC, nasopharyngeal cancers, multiple myeloma, non-Hodgkin's lymphoma and acute myeloid leukemia, or AML. We submitted an IND in January 2022 and received FDA clearance in February 2022. We may initiate a Phase 1 clinical trial in CD70-positive cancers, including RCC, pending other considerations, including data gathered by NovoCodex, who is also sponsoring clinical trials for the candidate and initiated a Phase 1 clinical trial in the second half of 2022. NovoCodex is the main sponsor of Phase 1 development of ARX305, and we will be reimbursed for our own internal development costs, up to a certain amount.

Our initial development focus for ARX305 is in RCC. Approximately 431,000 patients globally were diagnosed with RCC in 2020 and there were 179,000 associated deaths. In 2023, it is estimated that 81,000 new kidney-related cancer cases will be diagnosed, with 15,000 associated deaths. Based on U.S. data, the five-year survival rate, overall, is 76%, but just 14% if diagnosed with advanced disease. We believe more than half of these patients have tumors that overexpress CD70 to a level that enables targeted therapy with ARX305. Current therapies have relatively low response rates in RCC and there are currently no approved therapies for RCC that target CD70 overexpression.

Immuno-Oncology Conjugate Franchise

IOC therapies harness the power of the body's immune system to treat cancer. Unlike ADCs that use an antibody to deliver a cytotoxic payload to a cancer cell, IOCs modulate and direct the immune system, triggering a cascade reaction in order to kill a cancer cell. We believe our IOC product candidates are complementary and synergistic to our ADC franchise for treating cancer.

Our IOC franchise currently includes ARX102, a long-acting "alpha-off" smart IL-2 cytokine and our TLR7/8 ISAC program to stimulate the immune system. ARX102 is in IND-enabling studies pending data gathered by our partner Sino Biopharma, who is also sponsoring clinical trials for the product candidate. Sino Biopharma is expected to initiate a Phase 1 clinical trial for ARX102.

Collaborations

We have partnered with several pharmaceutical companies. We have existing product-specific global licenses with several pharmaceutical companies, including BeiGene, Ltd., or BeiGene; Sino Biopharma; NovoCodex and Elanco Animal Health. These collaborations have provided us with validation of our technology and non-dilutive capital in the form of upfront and milestone payments, as well as, in some instances, reimbursement of development expenses.

As of December 31, 2022, we had received an aggregate of \$285.5 million in upfront and milestone payments from our partners. Subject to the continued advancement of our partnered programs, we have the potential to receive additional clinical, regulatory, product approval, and sales-based milestones.

In August 2021, Bristol-Myers Squibb Company, or BMS, provided notice that it closed its Phase 2 clinical trial of FA-Relaxin Studies CV019-008 and CV019-010 based on internal considerations and not upon any observed safety concerns, and in February 2022, BMS provided written notice to terminate the FA-Relaxin collaboration and license agreement.

In November 2022, BeiGene provided notice of its intent to terminate the HER-3 ADC research program, effective January 2023. In March 2023, we and BeiGene extended the initial research term for an additional two years.

In 2023 and beyond, we may initiate and foster additional relationships with new partners worldwide to aide in the progression of our external product pipeline, including external development of ARX788.

Our Strategy

Our current focus is to discover and develop, both internally and externally through partnerships, a pipeline of ADCs to treat cancers, with an initial focus on cancers with a high unmet medical need. Our strategy to achieve this is to:

- ***Extend our leadership position in EPBs.*** We are pioneering SAA incorporation technologies, and we believe we are the only company utilizing this technology in both living bacterial and mammalian cell systems. This approach has generated a pipeline of EPBs with broad application and market potential. To maintain and extend our leadership position, we intend to continually invest in innovation to expand the capabilities of our proprietary technology platform and to further optimize the efficiency and reliability of our approach. We believe our leadership position is enhanced by our extensive industry experience in biologics as well as our strong intellectual property position. As we continue to develop our platform capabilities, we plan to expand and enhance our patent portfolio.
- ***Advance our proprietary ADC clinical program candidate, ARX517, through clinical development for the treatment of prostate cancer.*** ARX517 is the only PSMA ADC in clinical development. In the first half of 2021, we initiated a Phase 1 clinical trial for ARX517 for treating PSMA over-expressed cancer such as prostate cancer, especially in mCRPC. ARX517 has demonstrated potent *in vivo* anti-tumor efficacy in both enzalutamide sensitive and resistant prostate cancer models. A robust current good manufacturing practice, or cGMP, manufacturing process has been established, and the Phase 1 clinical trial materials have been manufactured. Dose escalation is ongoing, and we expect to have preliminary interim Phase 1 safety and efficacy data in the second half of 2023, which we expect will lead to a finding of a recommended dose that will allow us to initiate a Phase 1/2 clinical trial. We believe that ARX517, if ultimately approved, has the potential to be a first-in-class ADC targeting PSMA. Our clinical development strategy with respect to ARX517 is to focus on mCRPC and to evaluate solid tumor expansion.
- ***Continue to develop our ADC product candidate ARX788 in the post-Enhertu HER2-positive metastatic breast cancer population.*** Based, amongst other things and as described above, upon published data in China from ACE-Breast-01, preliminary data in the United States from ACE-Breast-03 and ACE-Pan-Tumor-01, which, in a small number of patients, shows anti-tumor activity in post-Enhertu, post-Kadcyla and HER2-low patients, we decided to conduct a signal-finding study in the HER2 positive post-Enhertu metastatic breast cancer patient population. Further, with the approval of Enhertu and its successful deployment in the second line, the third line treatment setting of metastatic breast cancer landscape has changed, and, given the clinical activity of ARX788, we believe that there may be significant opportunity for ARX788 in the third line treatment setting of HER2-positive metastatic breast cancer. This setting also may represent a significant commercial opportunity and, as such, we believe it is in our best interest to conduct a signal-finding study to determine if ARX788 has anti-tumor activity in the post-Enhertu patient population. Additionally, after ACE-Breast-02, the most advanced trial involving ARX788, demonstrated positive Phase 3 data in China, our decision that it would be in our best interest to continue internal development of ARX788, while redefining certain of the development characteristics, was further justified. We therefore plan to conduct a signal-finding study that will include a 2:1 randomization of ARX788 versus standard of care in approximately 45 additional HER2-positive post-Enhertu metastatic breast cancer patients under the previously paused Phase 2 ACE-Breast-03 study.
- ***Advance our proprietary ADC clinical program candidate, ARX788, through clinical development for HER2-positive breast and gastric cancer, including at the GEJ.*** In December 2020, the FDA granted ARX788 Fast Track designation as monotherapy for the treatment of advanced or metastatic HER2-positive breast cancer patients who have received one or more prior anti-HER2-based regimens in the metastatic setting. This designation supports our belief that ARX788 has the potential to address unmet medical needs for patients with HER2-positive breast cancers, including those tumors that can no longer be controlled by currently approved HER2-targeting therapies. In September 2021, Daiichi Sankyo released the DestinyBreast-03 clinical trial results, studying the activity of Enhertu compared to Kadcyla in second line treatment setting of metastatic breast cancer. With statistically significant and clinically meaningful improvement in the primary endpoint PFS over Kadcyla, both the National Comprehensive Cancer Network, or NCCN, and European Society for Medical Oncology, or ESMO, soon revised the

HER2-positive metastatic breast cancer treatment guideline to displace Kadcyla with Enhertu as the new standard of care in second line HER2-positive breast cancer. Accordingly, we revised our clinical plan to focus on studying ARX788 activity in breast cancer patients who have failed Enhertu. We plan to utilize the benefits of Fast Track designation, including more frequent interactions with the FDA and the ability to use rolling submissions for both biologics license applications, or BLAs, and supplemental BLAs, or sBLAs, to advance ARX788 for breast cancer through clinical development. In addition, we have ongoing collaborations with academic key opinion leaders to study ARX788 in early-stage HER2-positive breast cancer in the neoadjuvant setting and in HER2-low metastatic breast cancer. In January 2021, the FDA granted ARX788 Orphan Drug designation for the treatment of gastric cancer, including at the GEJ. In May 2021, the NMPA granted ARX788 Breakthrough Therapy designation for the second-line treatment of HER2-positive metastatic breast cancer. In December 2022, we announced encouraging preliminary efficacy and safety data from ACE-Breast-03 with respect to post-Kadcyla HER2-positive metastatic breast cancer patients, including 57.1% (4 of 7) ORR, 100% (7 of 7) DCR, and no observed drug-related SAEs. In March 2023, an interim analysis of a Phase 3 study, ACE-Breast-02, demonstrated that the study met its pre-specified interim primary efficacy endpoint with statistical significance, demonstrating a greater PFS benefit compared to the control.

- ***Expand the impact of ARX788 by advancing ARX788 clinical programs for other HER2-expressing or HER2-mutated tumors.*** Beyond breast and gastric/GEJ cancer, we believe that ARX788 may be effective across other HER2-overexpressing or HER2-mutated cancers, including NSCLC, urothelial, colorectal, ovarian, biliary tract and pancreatic cancers. In our preclinical studies we have observed ARX788's potential to treat HER2-low cancers. Additionally, we believe that our site-specific conjugation capabilities can create predictable and highly stable chemical bonds, which may reduce toxicity and make ARX788 an attractive candidate for use in combination with earlier-line standard of care therapeutics. These strategies may increase ARX788's addressable patient population, which could maximize patient impact and commercial opportunity.
- ***Continue to develop and expand our oncology-focused ADC and IOC franchises and platform technology.*** We recently advanced two ADC programs into the clinic including ARX517, an anti-PSMA ADC for prostate cancer, and, via NovoCodex, ARX305, an anti-CD70 ADC for CD70-positive renal, nasopharyngeal and other cancers. We believe our site-specific conjugation approach could provide a wider therapeutic index than existing therapies for these cancers and achieve more efficacious doses in humans while reducing toxicity concerns. Further, our IOC franchise, with three additional early-stage product candidates targeting various cancers, offers a different and complementary approach to our ADC franchise. The Phase 1 first-in-human study for ARX517 was started in July 2021, and the Phase 1 first-in-human study for ARX305 began in the second half of 2022 when our partner, NovoCodex, dosed the first patient in China. Our platform technology underpins both franchises and by sharing payload technologies that have been tested in clinical trials, we have the potential to reduce development time, cost and risk. We plan to leverage our platform to selectively add new franchises to our product pipeline, such as immunology and infectious disease, designed to address critical healthcare problems with large unmet medical needs.
- ***Maximize the potential of our pipeline and technology platform by selectively entering strategic collaborations or partnerships and facilitating development of the product candidates in our external pipeline.*** We retain development and commercialization rights to all programs in our ADC and IOC franchises in most major markets, excluding China. To support these programs, we intend to build internal development capabilities where appropriate and use strategic collaborations and partnerships elsewhere to accelerate development and maximize commercial potential. On a program-by-program basis, we plan to selectively explore partnerships with biopharmaceutical companies possessing complementary capabilities in research, development, therapeutic area, geographical, or commercial expertise.

Our Product Pipeline

Our product pipeline consists of differentiated and novel product candidates in clinical and preclinical development stages, spanning our ADC franchise, IOC franchise, and partnered or out-licensed programs. We intend to drive future pipeline expansion through our innovative technology platforms and selective partnerships with pharmaceutical companies.

ARX517 (PSMA ADC)

ARX517 is an anti-PSMA ADC that has received FDA IND clearance and is recently ongoing in dose escalation Phase 1 clinical trial for mCRPC. PSMA is a clinically important biomarker of prostate cancer, particularly highly over-expressed in mCRPC. PSMA is also widely expressed in the neovasculature of other solid tumors, such as pancreatic, NSCLC and ovarian, making it an attractive target for ARX517.

Although recently approved therapies provide a survival benefit, not all patients respond, and in general those who do respond eventually develop resistance and experience disease progression. Therefore, there is still a strong and urgent medical need for new therapeutic modalities for mCRPC patients. Moreover, there is no therapy approved for PSMA-positive prostate cancer. A PSMA ADC would provide a different mechanism of action and could potentially offer benefits over existing therapies. However, early anti-PSMA ADC efforts often failed due to linker-payload instability leading to off-target toxicity issues. In order to address these issues, we have utilized our site-specific conjugation technology platform to create a single optimized structure with our proprietary AS269 payload. Specifically, we have designed ARX517 to have enhanced payload stability, which may provide a wider therapeutic window, thereby resulting in greater therapeutic benefit and reduced toxicity concerns.

In preclinical studies of ARX517 in mCRPC, anti-tumor effects were demonstrated in multiple tumor cell lines and models, including prostate cancer models sensitive and resistant to anti-androgen treatments such as enzalutamide. These results supported our decision to advance ARX517 into a Phase 1 clinical trial.

Summary of ARX517 Clinical Development Strategy

We received FDA IND clearance for ARX517 in October 2020 for a Phase 1a clinical trial in mCRPC and other solid tumors with PSMA over-expression.

The combination of ARX517's specificity for PSMA, potent preclinical anti-tumor activity, payload stability, and potential to target a broad range of PSMA-expressing tumors supports the clinical development of ARX517 in prostate cancer and other solid tumors.

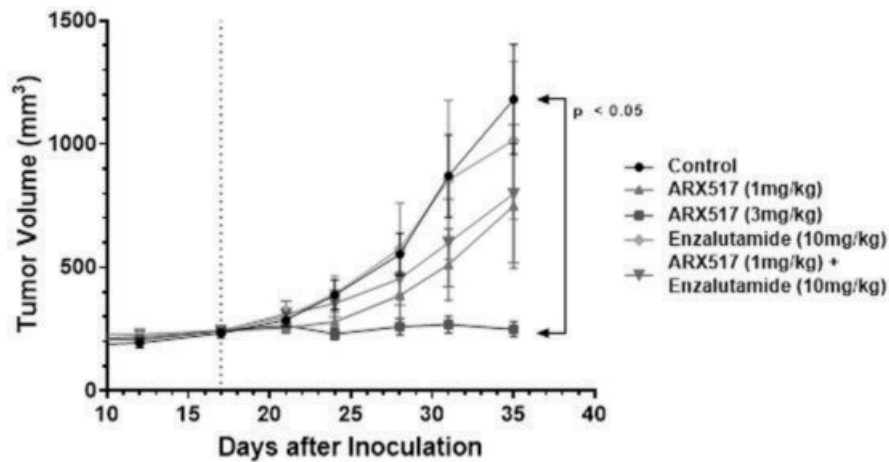
The multi-center, open-label, first-in human Phase 1 trial is ongoing in the United States. This trial, referred to as APEX-01, is primarily designed to assess the safety, tolerability and PK profile, and secondarily the anti-tumor activity of ARX517 as a monotherapy and to identify the RP2D. The trial aims to enroll up to 76 patients with advanced solid tumors whose diseases have failed prior standard therapies and clinical site activation began in April 2021. As of February 2023, we have dosed patients across seven dose level cohorts starting from 0.32 mg/kg to 2.4 mg/kg. Dose escalation is ongoing, and an analysis of initial preliminary data from the trial provided early evidence of proof of concept for single-agent ARX517 as an ADC treatment for advanced prostate cancer. ARX517 has been well-tolerated, with Grade 1 or 2 treatment-related AEs being reported. The maximum tolerated dose has not yet been reached. No drug-related SAEs or DLTs have been observed, and no Grade 3 or greater treatment-related AEs have been observed. We anticipate preliminary interim safety and efficacy data in the second half of 2023.

Summary of ARX517 Preclinical Studies

Our preclinical studies of ARX517 have shown potent anti-tumor activity in *in vivo* models. These studies included evaluating anti-tumor activity of ARX517 in both a prostate cancer cell line derived xenograft model and a patient sample derived PDX tumor model.

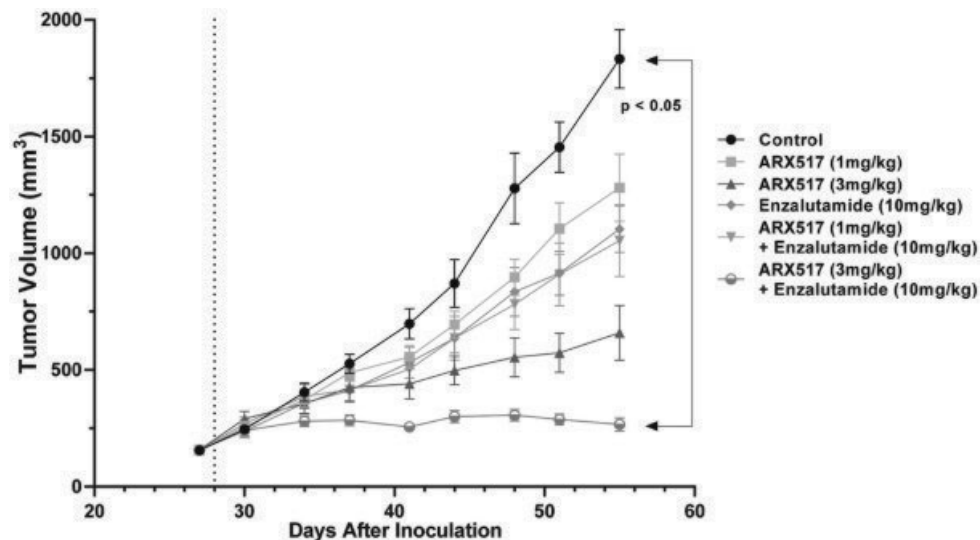
As shown in the figure below, in an enzalutamide-resistant PSMA-expressing C4-2 prostate cancer model, weekly dosing of ARX517 at 3 mg/kg resulted in potent tumor inhibition, while enzalutamide showed no significant activity.

In Vivo Activity of ARX517 in Enzalutamide-resistant C4-2 Prostate Cancer Xenograft Model



In an enzalutamide-sensitive prostate cancer PDX model (TM00298), ARX517 in combination with enzalutamide induced greater tumor inhibition than either of the single-agent arms, demonstrating a potential for combination therapy. All treatments were well-tolerated, and mice experienced no weight loss in any treatment group.

In Vivo Activity of ARX517 in Prostate Cancer PDX Model



IND-enabling studies were conducted to evaluate potential toxicity risks prior to human studies and to estimate starting doses for clinical trials. Key IND-enabling studies included pharmacology, PK and toxicology assessments. The preclinical dosing route and frequency of administration paralleled proposed dosing in human clinical trials. The overall IND-enabling results supported the study of ARX517 in humans.

ARX788

ARX788, an anti-HER2 ADC currently in a Phase 3 clinical trial (ACE-Breast-02) for the treatment of HER2-positive metastatic breast cancer, is intended to enable registration in China and a Phase 2/3 clinical trial (ACE-Gastric-02) in patients with HER2-positive gastric/GEJ cancer intended to enable registration in China as well as additional countries. In a Phase 1 clinical trial in HER2-positive breast cancer (ACE-Breast-01), ARX788 has generally been well-tolerated to date, with two drug-related SAEs reported, and achieved a confirmed ORR of 66% (19 of 29 patients) and a DCR of 100% in the cohort of patients receiving the 1.5 mg/kg at Q3W dose, and a confirmed ORR of 50% (8 of 16 patients) and a DCR of 88% in the cohorts of patients receiving the 1.3 mg/kg at Q3W or Q4W doses, as of December 13, 2021. Enrollment in ACE-Breast-02 has completed, and the study has met its pre-specified interim primary efficacy endpoint with statistical significance, demonstrating a greater PFS benefit compared to the active control.

As stated above, on October 18, 2022, we announced a reprioritization of our product pipeline after conducting a strategic assessment that considered our cash runway and our product pipeline's near term value creation opportunities, among other factors. As a result of our assessment, we paused the internal development of ARX788 and, among other potential activities, may seek development partners to further its development outside of China.

As stated above, during the first quarter of 2023, we decided to conduct a signal-finding study in the post-Enhertu metastatic breast cancer patient population. This decision was based, amongst other things, upon published data in China from ACE-Breast-01, preliminary data in the United States from ACE-Breast-03 and ACE-Pan-Tumor-01, which, in a small number of patients, shows anti-tumor activity in post-Enhertu, post-Kadcyla and HER2-low patients. Further, with the approval of Enhertu and its successful deployment in the second and third line treatment setting of metastatic breast cancer landscape has changed, and, given the clinical activity of ARX788, we believe that there may be significant opportunity for ARX788 in the third line treatment setting of HER2-positive metastatic breast cancer. This setting, as well as potentially additional opportunities for ARX788 should Enhertu be approved as a treatment for breast cancer in earlier lines of therapy, may represent a significant commercial opportunity. As such, we believe it is in our best interest to conduct a signal-finding study to determine if ARX788 has anti-tumor activity in the post-Enhertu patient population.

Additionally, as stated above, our decision to continue the internal development of ARX788 was reinforced following the announcement from NovoCodex that ACE-Breast-02, the most advanced trial involving ARX788, demonstrated positive Phase 3 data in China. In light of these factors, we plan to conduct a signal-finding study that will include a 2:1 randomization of ARX788 versus standard of care in approximately 45 additional HER2-positive post-Enhertu metastatic breast cancer patients as an amendment to and under the previously paused Phase 2 ACE-Breast-03 study protocol.

We believe ARX788 has the potential to significantly improve outcomes for HER2-positive cancers, including in patients with metastatic disease and in earlier stages, such as the adjuvant and neoadjuvant settings. Our initial focus is on the treatment of patients with HER2-positive breast and gastric cancer, including at the GEJ. However, we believe ARX788 may benefit a broader spectrum of cancer patients, including HER2-low breast cancer patients where no targeted treatment is available, as well as HER2-positive and HER2-low patients in other malignancies, such as NSCLC, biliary tract, urothelial, colon, ovarian and pancreatic cancers. We plan to conduct a signal-finding study that will include a 2:1 randomization of ARX788 versus standard of care in approximately 45 HER2-positive post-Enhertu metastatic breast cancer patients under the previously paused Phase 2 ACE-Breast-03 study, while redefining certain of the development characteristics.

Clinical Overview of ARX788

In ongoing Phase 1 clinical trials of ARX788 for the treatment of HER2-positive cancers, we observed promising anti-tumor activity in heavily pre-treated cancer patients at the 1.5 mg/kg and 1.3 mg/kg doses. Highlights from clinical trials of ARX788 include:

- Confirmed ORR of 66% (19 of 29 patients) and DCR of 100% in the 1.5 mg/kg cohort and confirmed ORR of 50% (8 of 16 patients) and DCR of 88% in the 1.3 mg/kg cohorts, in the ACE-Breast-01 trial.
- Confirmed ORR of 67% (2 of 3 patients) and DCR of 100% (3 of 3 patients) in the 1.5 mg/kg dose escalation cohort, and no confirmed responses (0 of 8 patients) and DCR of 100% (8 of 8 patients) in the 1.3 mg/kg dose escalation cohort, in the ACE-Pan-Tumor-01 trial.
- Confirmed ORR of 43% (3 of 7 patients) in the 1.7 mg/kg cohort, 46% (6 of 13 patients) in the 1.5 mg/kg dose escalation cohort and confirmed ORR of 43% (3 of 7 patients) in the 1.3 mg/kg cohort, in the ACE-Gastric-01 trial.
- Confirmed ORR of 57.1% by RECIST v1.1 and DCR of 100% after treatment with ARX788 in HER2-positive metastatic breast cancer patients who are resistant or refractory to T-DM1, in the ACE-Breast-03 trial.
- Anti-tumor activity observed in patients with tumors resistant and refractory to approved HER2-targeting regimens.
- The median duration of response, or mDOR, at the 1.5 mg/kg dose and 1.3 mg/kg dose was 14.4 months and 12.9 months, respectively, and the median PFS at the 1.5 mg/kg dose was 17 months in the ACE-Breast-01 trial.
- Generally well-tolerated with most AEs being mild (Grade 1) or moderate (Grade 2) and manageable with a few drug-related SAEs in the aggregate reported from the patients dosed with ARX788 in the ACE-Breast-01, ACE-Pan-Tumor-01 and ACE-Gastric-01 trials.
- The systemic toxicity (such as neutropenia, thrombocytopenia, anemia, decreased white blood cell counts, nausea, vomiting, constipation, diarrhea, neuropathy, fatigue, dizziness and headache) observed in the ACE-Breast-01, ACE-Pan-Tumor-01 and ACE-Gastric-01 trials has been low in terms of the incidence rate and grade.
- AEs of special interests, or AESIs, included pneumonitis/ILD, ocular AEs, and ALT/AST increase. As previously reported, we have observed distinct differences in AESI distribution between the Chinese (ACE-Breast-01, ACE-Breast-02 and ACE-Gastric-01) and United States/Australia (ACE-Pan-Tumor-01 and ACE-Breast-03) patient population. Distribution of AESI of ILD/pneumonitis between studies conducted in China and United States/Australia have been reported to be higher in China (approximately 25%) compared to the United States/Australia (approximately 8%). This difference could be attributed to management of ILD/pneumonitis within each protocol and/or country, country-specific health and/or socio-economic factors, and prevalence of COVID-19 related disease. While Grade 5 toxicity related to ILD/pneumonitis have been reported in China, no Grade 4 or Grade 5 AESIs related to ILD/pneumonitis has been reported in United States/Australia.

Summary of ARX788 Clinical Results

ACE-Breast-01: Phase 1 Clinical Trial for HER2-positive Breast Cancer in China

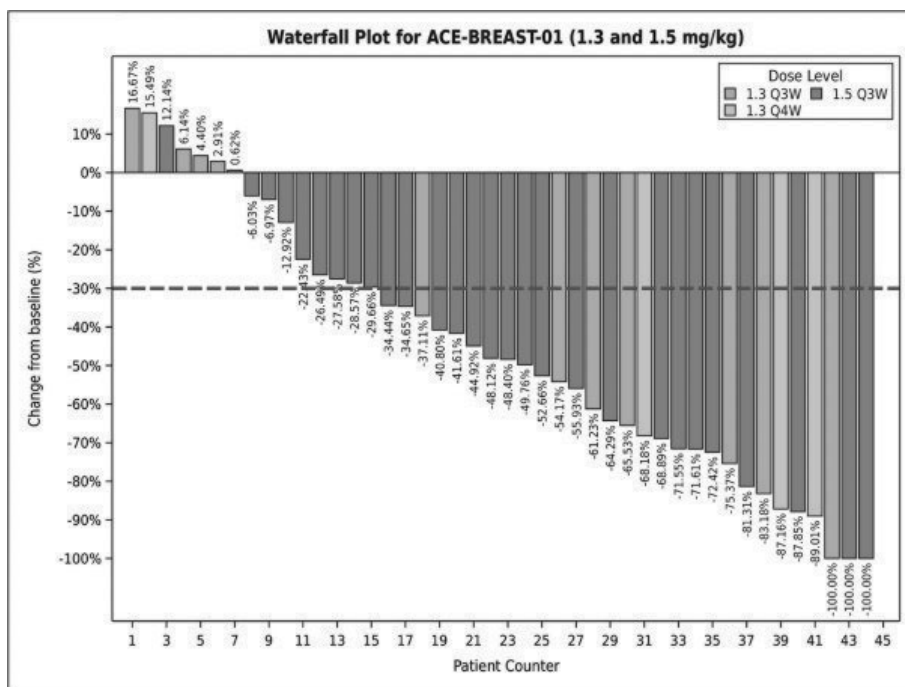
ACE-Breast-01, being conducted by our partner, NovoCodex, is an ongoing Phase 1 dose escalation trial in China in patients with HER2-positive advanced or metastatic breast cancer whose diseases have failed multiple prior lines of therapy. ACE-Breast-01 was designed to assess the safety, tolerability and PK profile, as well as the anti-tumor activity of ARX788 and to identify the recommended Phase 2 dose, or RP2D. This trial, with a 3+3 escalation design, has dosed patients from 0.33 mg/kg at Q3W up to 1.5 mg/kg at Q3W, with dose expansion starting at the 1.1 mg/kg at Q3W dose. The patients that have been enrolled in ACE-Breast-01 were heavily pre-treated, with a median of six prior lines of therapy (range of 2 to 17). As of the data cut-off date of December 14, 2021, a total of 69 patients were response-evaluable, and 29 patients were response-evaluable at the 1.5 mg/kg Q3W dose. Preliminary efficacy data by dose cohort from this clinical trial is described below.

Summary of ARX788 ACE Breast-01 Preliminary Data

In this trial, ARX788 has demonstrated a 66% (19 of 29 patients) confirmed ORR and 100% DCR in the 1.5 mg/kg cohort and a 50% (8 of 16 patients) confirmed ORR and 88% DCR in the 1.3 mg/kg cohorts. The waterfall plot below shows the best change in the sum of the target lesions from baseline in the 1.5 mg/kg and 1.3 mg/kg cohorts. Total of five patients, including three patients in the 1.5 mg/kg cohort, one patient in the 1.3 mg/kg at Q3W cohort and one patient in the 1.3 mg/kg Q4W cohort, achieved 100% reduction of the target lesions. ARX788 has been generally well-tolerated, with most AEs being mild (Grade 1) or moderate (Grade 2) and generally manageable. There have been a few drug-related SAEs (pneumonitis and platelet count decreased) reported in the ACE-Breast-01 trial.

The safety and efficacy data from ACE-Breast-01 were presented at the SABCS 2021, and is published in Clinical Cancer Research ((2022) 28 (19): 4212–4221 (Zhang, et al.).

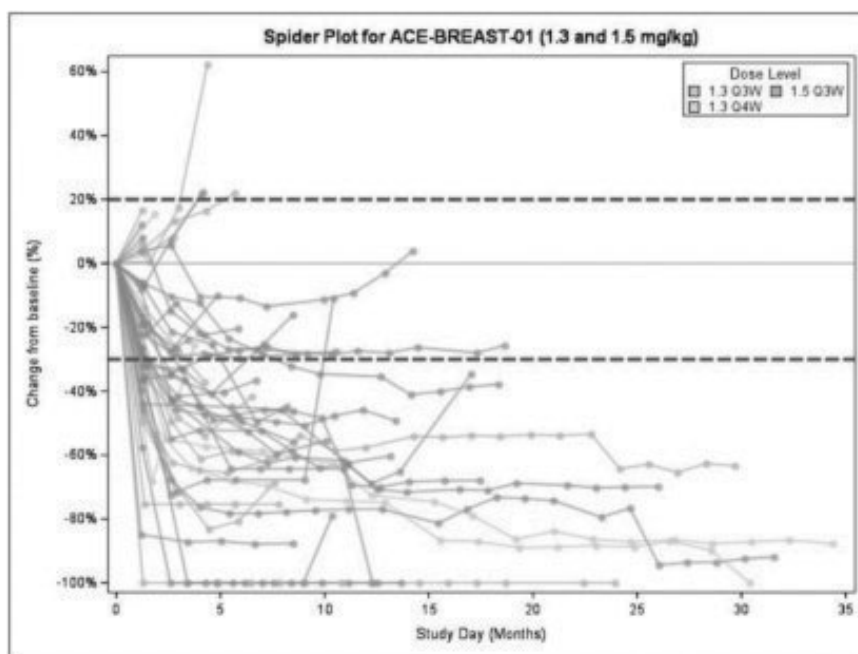
Best Change in Sum of Target Lesions



(Data as of December 14, 2021)

In the 1.5 mg/kg and 1.3 mg/kg cohorts, ARX788 has demonstrated the potential for rapid, deep and durable tumor responses. The spider plot below depicts the change in the sum of target lesions from baseline over time.

Change in Sum of Target Lesions



(Data as of December 14, 2021)

Summary of ACE-Breast-01 Confirmed ORR in patients whose disease is resistant or refractory to prior HER2 treatment (trastuzumab, ADCs, TKIs, and bispecific antibodies) at ARX788 1.5 mg/kg Q3W

Prior anti-HER2 therapy	Confirmed ORR
Trastuzumab containing regimens	19/29 (66%)
HER2 ADCs (T-DM1, DX126-262, A166, BAT8001, and HS630) regimens	4/5 (80%)
HER2 TKIs (lapatinib, pyrotinib, neratinib, AST-1306, and Hmays-022) regimens	15/23 (65%)
Both HER2 ADC and HER2 TKI regimens	3/4 (75%)
Bispecific antibodies (KN026 and M802) containing regimens	3/4 (75%)

As shown in the table above, at the 1.5 mg/kg dose level, ARX788 had robust anti-tumor activity in patients whose disease was resistant/refractory to other HER2-targeted therapies, with confirmed ORR ranging from 65% to 80%.

The trial completed enrollment of 69 patients and database lock occurred after six months' follow-up. Based on the data from this ongoing trial and regulatory feedback received in China to date, our partner, NovoCodex, initiated ACE-Breast-02, a potentially registrational Phase 3 clinical trial for the treatment of HER2-positive breast cancer in China and based on the data from ACE-Gastric-01 trial, a potentially registrational Phase 2/3 trial, ACE-Gastric-02, for the treatment of HER2-positive gastric/GEJ cancer in China and for which we intend to partner with companies outside of China to subsequently enroll patients in additional countries, after submission of clinical trial applications for those jurisdictions.

We initiated ACE-Breast-03, a global, potentially pivotal Phase 2 trial for HER2 positive metastatic breast cancer, for which we expect to provide a preliminary clinical data update in 2024. Enrollment for the trial has been paused, but patients already enrolled continued being treated. We plan to amend the protocol under the study to conduct a signal-finding study that will include a 2:1 randomization of ARX788 versus standard of care in approximately 45 HER2-positive post-Enhertu metastatic breast cancer patients, while redefining certain of the development characteristics.

ACE-Breast-02: A China Phase 3 Clinical Trial for HER2-positive Breast Cancer

NovoCodex initiated ACE-Breast-02, a Phase 3 randomized trial of ARX788 in HER2-positive advanced breast cancer. Dosing began in September 2020 in China. ACE-Breast-02 trial plans to enroll a total of 440 subjects with HER2-positive advanced breast cancer, who have previously received first-line treatment of trastuzumab and less than two lines of chemotherapy. Target enrollment was 440 patients. Subjects will be randomized in a 1:1 ratio and will receive ARX788 1.5 mg/kg at Q3W in the treatment arm or lapatinib plus capecitabine in the control arm. An Independent Data Monitoring Committee, or IDMC, conducted an interim analysis and concluded that the ACE-Breast-02 study met its pre-specified interim primary efficacy endpoint with statistical significance, demonstrating a greater PFS benefit compared to the control. Results gathered so far demonstrate that ARX788 has been generally well-tolerated. There have been reported drug-related SAEs (pneumonitis, pneumonia, interstitial lung disease, respiratory failure, platelet count decreased, asthenia, pulmonary embolism and alanine aminotransferase increased). As previously reported and stated above, we have observed distinct differences in AESI distribution between the Chinese (ACE-Breast-01, ACE-Breast-02 and ACE-Gastric-03) and the United States/Australia (ACE-Pan-Tumor-01 and ACE-Breast-03) population. Distribution of AESI of ILD/pneumonitis between studies conducted in China and the United States/Australia have been reported to be higher in China (approximately 25%) compared to the United States/Australia (approximately 8%). This difference could be attributed to management of ILD/pneumonitis within each protocol and/or country, country-specific health and/or socio-economic factors, and prevalence of COVID-19 related disease. While Grade 5 toxicity related to ILD/pneumonitis has been reported in China, no Grade 4 or Grade 5 AESIs related to ILD/pneumonitis have been reported in United States/Australia. Based on the results from ACE-Breast-02, NovoCodex plans to submit a communication application to seek marketing approval in China pending discussion with the NMPA.

ACE-Breast-03: A Global Phase 2 Clinical Trial for HER2-positive Breast Cancer (now paused)

We initiated ACE-Breast-03, a Phase 2 potentially registrational single-arm global trial of ARX788 in HER2-positive metastatic breast cancer patients whose diseases have failed T-DM1, and/or T-DXd, and/or tucatinib-containing regimens. The study is being conducted in the United States, Korea, and Australia, and target enrollment in the trial was 210 patients. Following our analysis of data from ongoing Phase 1 clinical trials of ARX788 at the 1.5 mg/kg and 1.3 mg/kg doses using ARX788 of frozen liquid formulation, including the totality of the efficacy, safety and PK data, as well as discussion of the protocol with the FDA, we initially determined the dosing regime in this trial would consist of an initial loading dose of 1.5 mg/kg, followed by 1.3 mg/kg Q4W maintenance doses based on data using ARX788 of frozen liquid formulation with the intent to transition into our more commercially viable lyophilized powder formulation later.

To adopt a more commercially viable lyophilized powder formulation with an optimized dose, we conducted PK modeling and simulation which suggested that the exposure with the lyophilized powder is slightly lower than the frozen liquid formulation at the same dose. Based on this observation as well as of a more favorable ex-China AESI safety profile, we amended our current protocol to version 2.0 to include a safety lead-in cohort with approximately 10 subjects per dose (1.6 and 1.7 mg/kg Q3W) added before main trial starts.

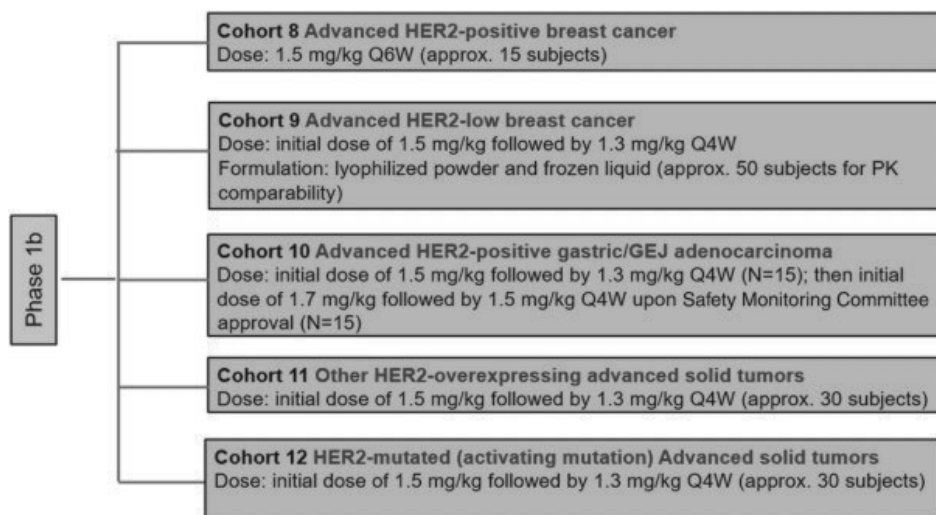
Enrollment in ACE-Breast-03 has been paused, and preliminary data was presented during a Spotlight Poster Presentation at the SABCS 2022. The preliminary results presented at SABCS 2022 demonstrated 57.1% confirmed ORR by RECIST v1.1 and 100% DCR in heavily pre-treated post-Kadcyla patients with HER2-positive metastatic breast cancer following treatment with ARX788. None of the patients experienced drug-related SAEs and all AEs were well tolerated. Patients that were enrolled in ACE-Breast-03 prior to enrollment being paused continue to be treated. We expect to provide a preliminary clinical data update in 2024. We also plan to conduct a signal-finding study that will include a 2:1 randomization of ARX788 versus standard of care in approximately 45 HER2-positive post-Enhertu metastatic breast cancer patients under the previously paused Phase 2 ACE-Breast-03 study, while redefining certain of the development characteristics.

ACE-Pan-Tumor-01: A Phase 1 Clinical Trial for HER2-positive Cancers in the United States and Australia (now paused)

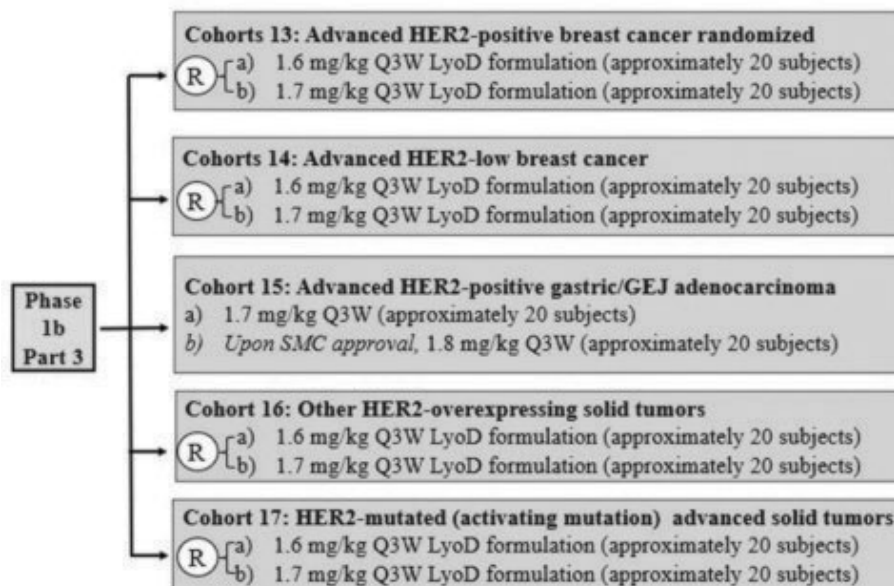
ACE-Pan-Tumor-01 includes a Phase 1 dose escalation trial in HER2-expressing solid tumors (including breast cancer, gastric/GEJ, NSCLC, ovarian, colorectal, biliary tract, urothelial, endometrial, and salivary gland cancers) in the United States and Australia. ACE-Pan-Tumor-01 is designed to assess the safety, tolerability and PK profile as well as the anti-tumor activity of ARX788 as a monotherapy and to identify the RP2D. ARX788 has been generally well-tolerated in the ACE-Pan-Tumor-01 trial, with most AEs being mild (Grade 1) or moderate (Grade 2) and generally manageable. There have been a few drug-related SAEs (pneumonitis, dyspnoea, pneumonia parainfluenzae viral, hyperuricaemia and hypokalaemia) in the ACE-Pan-Tumor-01 trial. The trial has dosed patients from 0.66 mg/kg at Q3W up to 1.5 mg/kg at Q3W following a 3+3 escalation design. As of December 14, 2021, the enrollment of Phase 1a was completed. A total of 28 patients enrolled in the dose escalation. In the 1.5 mg/kg cohort, ARX788 had demonstrated a 67% (2 of 3 patients) confirmed ORR and a 100% DCR. Preliminary efficacy data by dose cohort from this clinical trial is presented in the table below. Additionally, we have observed anti-tumor activity in patients with tumors resistant and refractory to other HER2-targeting ADCs, such as T-DM1 or T-DXd.

Summary of ARX788 ACE-Pan-Tumor-01 Dose Escalation (Phase 1a) Preliminary Data

ARX788 ACE-Pan-Tumor-01 Dose Expansion Cohorts 8 through 12



We initiated the Phase 1b part of our ACE-Pan-Tumor-01 trial. As part of the effort to quickly adopt the more commercially viable lyophilized powder formulation, we amended the Phase 1b protocol shown above to Part 3 as shown in the diagram below. The data from cohorts 13, 14, 15A, 16 and 17 which plans to study at 1.6 or 1.7 mg/kg for lyophilized powder formulation, will be used, together with data from the ACE-Breast-03 trial, to determine the RP2D. In addition, the safety and efficacy data obtained from cohort 14 will guide us in the future design of any clinical trials for HER2-low breast cancer. In October 2022, enrollment in ACE-Pan-Tumor-01 was paused for the strategic reprioritization reasons we announced at that time, and we expect to have an update on the preliminary data by the end of 2023. Patients that were enrolled in the study prior to enrollment being paused continue to be treated.



ACE-Gastric-02: A China Phase 2/3 Clinical Trial for HER2-positive Advanced Gastric Cancer, Including at the GEJ

NovoCodex initiated ACE-Gastric-02, a pivotal Phase 2/3 randomized trial of ARX788 in HER2-positive advanced gastric and GEJ cancer. Dosing began in August 2021 in China. The ACE-Gastric-02 trial plans to enroll a total of 405 subjects with HER2-positive advanced gastric or GEJ cancer, who have previously received first-line treatment and experienced progressive disease during or after trastuzumab treatment. Subjects will be randomized in a 2:1 ratio and will receive ARX788 1.7 mg/kg at Q3W or the treating physician's choice of second-line, standard-of-care treatment per local guidelines in China. The ARX788 dosing regimen for ACE-Gastric-02 was determined by NovoCodex based on an analysis of existing anti-tumor activity, tolerability and exposure data in the intended gastric cancer patient population, in which patients typically have lower exposure to antibody and ADC treatments compared to breast cancer. ARX788 has been generally well-tolerated, with most AEs being mild (Grade 1) or moderate (Grade 2) and generally manageable. There have been a few drug-related SAEs (interstitial lung disease and blurred vision) reported in the ACE-Gastric-01 trial.

Summary of ARX788 Clinical Development Strategy

Based on the encouraging tolerability profile and anti-tumor activity observed in preclinical studies and ongoing clinical trials, we have developed the following clinical strategies to pursue applications for accelerated approval of ARX788 and expand its cancer indications and geographic reach:

- **Pursue indications with the greatest unmet medical needs to improve the lives of breast cancer patients.** We, together with our partner, are conducting or plan to conduct potentially pivotal trials in HER2-positive breast cancer patients whose disease can no longer be controlled by currently approved HER2-targeting therapies, including Enhertu. In addition to the clinical trials discussed herein, we may conduct trials in HER2-low metastatic breast cancer and advanced breast cancer with brain metastases.
- **Leverage the anti-tumor activity and tolerability profile of ARX788 and potentially move into earlier lines of therapy for breast cancer and seek combination therapy with other agents.** We may conduct randomized head-to-head trials against T-DM1 in HER2-positive metastatic breast cancer. We may also conduct trials in combination with synergistic agents from other potential collaborators to investigate the ability to improve therapeutic effects in difficult-to-treat patient populations.
- **Expand ARX788's clinical impact beyond breast cancer by conducting trials in additional HER2-overexpressing or HER2-mutated cancers.** Our partner, NovoCodex, is conducting trials in HER2-positive gastric/GEJ. We may explore other HER2-overexpressing or HER2-mutated tumors, such as NSCLC, urothelial, colon, ovarian, biliary tract or pancreatic cancers.
- **Continue to pursue expedited regulatory programs.** In December 2020, the FDA granted ARX788 Fast Track designation as monotherapy for the treatment of advanced or metastatic HER2-positive breast cancer patients who have received one or more prior anti-HER2-based regimens in the metastatic setting. In January 2021, the FDA granted ARX788 Orphan Drug designation for the treatment of gastric cancer, including cancer at the GEJ, and in May 2021, the NMPA granted ARX788 Breakthrough Therapy designation for the second-line treatment of HER2-positive metastatic breast cancer. NovoCodex plans to submit a communication application to seek marketing approval in China pending discussion with NMPA. We plan to continue to explore other programs that may accelerate the registration of ARX788.

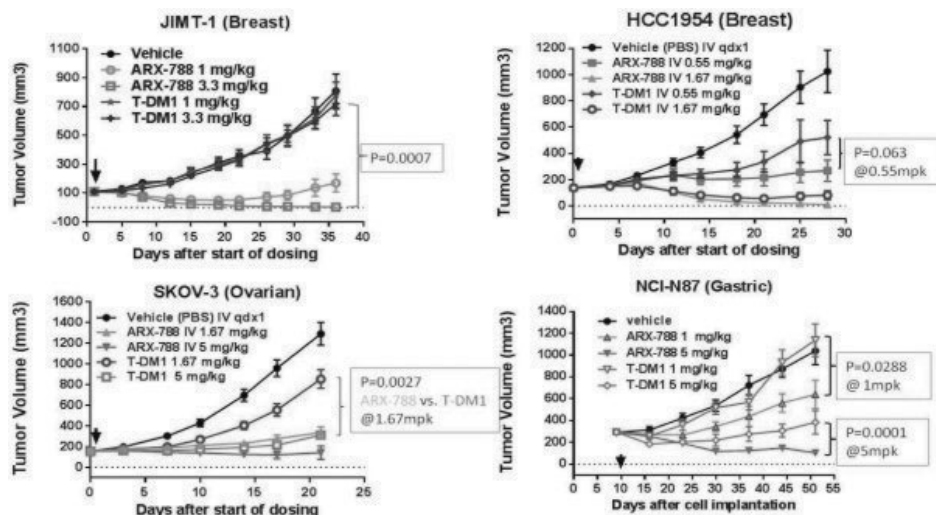
Summary of ARX788 Preclinical Studies

ARX788 has shown promising anti-tumor activity in a wide range of preclinical cancer models that include high- and low-HER2-expressing breast cancers, ovarian cancer and gastric cancer. In head-to-head preclinical models, ARX788 has demonstrated greater anti-tumor activity as a single agent compared to T-DM1 in HER2-positive cancers, as well as synergistic activity when combined with other cancer therapies. The key findings from our preclinical studies, which we believe support our decision to develop ARX788 as a single agent and in combination with standard of care therapies in clinical trials, are summarized below:

1. **Enhanced anti-tumor activity in preclinical studies as a single agent compared to T-DM1 in HER2-positive cancers**, highlighting the potential to more effectively treat patients with T-DM1 resistant tumors.
2. **Encouraging single-agent anti-tumor activity in both high- and low-HER2-expressing cancer models**, which may provide the basis for us to expand into HER2-low patients and more difficult to treat HER2 related diseases such as gastric and ovarian cancers.
3. **Enhanced anti-tumor activity when combined with an anti-PD-1 and other agents such as HER2 TKI**, highlighting the potential for increased efficacy in combination with other cancer therapies and the benefit of a potentially wider therapeutic index.
4. **Improved tolerability profile in preclinical studies when compared to a conventional cysteine-conjugated HER2 ADC**, highlighting the potential of our platform to create engineered homogeneous antibodies (DAR of 2) with more stable payloads.

We have assessed ARX788 in several breast cancer models. JIMT-1 is a low-HER2 expressor in which T-DM1 showed no activity, while ARX788 completely inhibited tumor growth. As shown in the figure below, ARX788 demonstrated better tumor suppression than T-DM1 when used at the same dose in all three cancer models of HER2-high expression: HCC1954 breast cancer, SKOV-3 ovarian cancer, and NCI-N87 gastric cancer. Collectively, these data suggest heightened activity of ARX788 across a wider level of HER2-expression when compared to T-DM1. The figures below depict an approximate three-fold increase in single agent anti-tumor activity for ARX788 over T-DM1 in all three HER2-high xenograft models. Those data imply that ARX788 has the potential to treat a broad panel of HER2-high cancers such as breast, gastric and ovarian cancer, as well as HER2-low breast cancer.

Anti-tumor Activity of ARX788 in Xenograft Models of Different HER2-Expressing Cancers

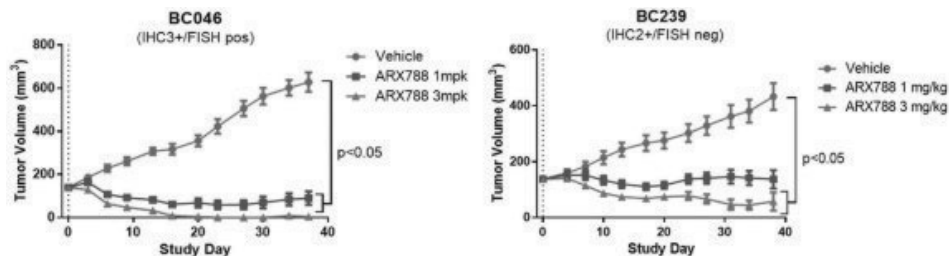


In addition, ARX788 was tested in multiple breast cancer patient-derived xenograft, or PDX, models. As shown in the figure below, a single dose of ARX788 at 1 mg/kg demonstrated robust anti-tumor activity in three of six HER2-high expression PDX models as measured by tumor growth inhibition, or TGI. In HER2-low expression PDX models, ARX788 also demonstrated robust anti-tumor activity, confirming the results observed in the xenograft model studies.

Anti-tumor Activity of ARX788 in Breast Cancer PDX Models

	BC PDX models	HER2 status	Route /Schedule	TGI
HER2 High	BC#013	HER2 pos (FISH+; IHC3+)	IV: QD x1	85% (1 mg/kg) 92% (3 mg/kg)
	BC#046	HER2 pos (FISH+; IHC3+)	IV: QD x1	84% (1 mg/kg) 99% (3 mg/kg)
	BC#197	HER2 pos (FISH+; IHC3+)	IV: QD x1	66% (1 mg/kg) 91% (3 mg/kg)
	BC#128	HER2 pos (FISH+; IHC3+)	IV: QD x1	-25% (1 mg/kg) 47% (3 mg/kg)
	BC#207	HER2 pos (FISH+; IHC3+)	IV: QD x1	18% (1 mg/kg) 20% (3 mg/kg)
	BC#058	HER2 pos (FISH-; IHC3+)	IV: QD x1	20% (1 mg/kg) 38% (3 mg/kg)
HER2 Low	BC#085	HER2 low (FISH-; IHC2+)	IV: QD x1	42% (1 mg/kg) 57% (3 mg/kg)
	BC#239	HER2 low (FISH-; IHC2+)	IV: QD x1	68% (1 mg/kg) 87% (3 mg/kg)

ARX788 in HER2 High (BC046) and HER2 Low (BC239) PDX Breast Cancer Models

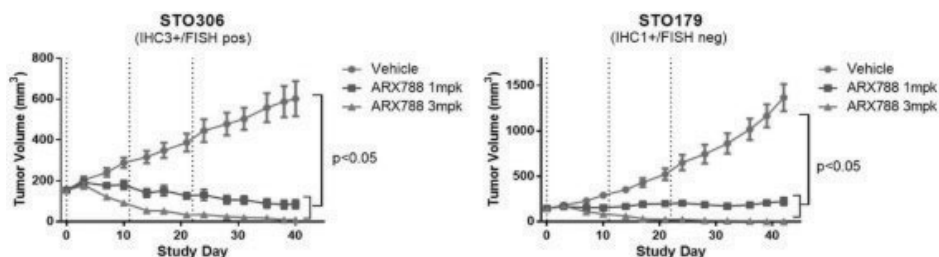


In addition to breast cancer, ARX788 was evaluated in 12 human gastric cancer PDX models. As shown in the table and figure below, potent anti-tumor activity was demonstrated in all HER2-high models and, importantly, robust anti-tumor activity was demonstrated with HER2-low patient samples as well.

Anti-tumor Activity of ARX788 in Gastric Cancer PDX Models.

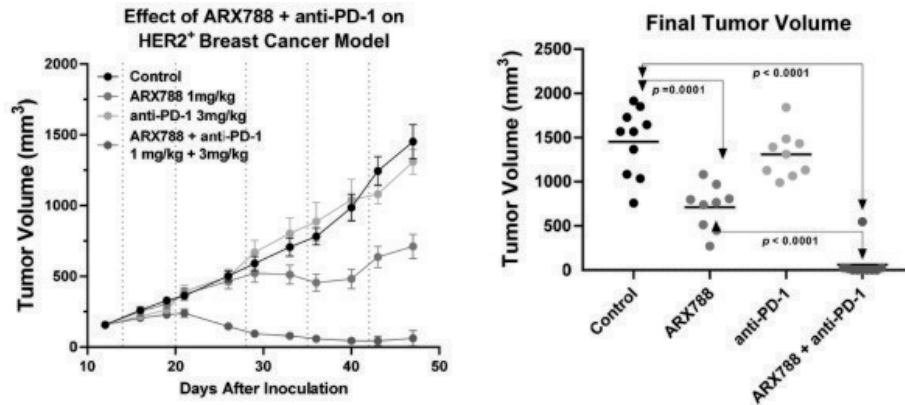
	GC PDX models	HER2 status	Route /Schedule	TGI
HER2 High	STO#041	HER2 pos (FISH+; IHC3+)	IV: QD x1	43% (3 mg/kg) 96% (10 mg/kg)
	STO#069	HER2 pos (FISH+; IHC3+)	IV: QD x1	35% (3 mg/kg) 100% (10 mg/kg)
	STO#410	HER2 pos (FISH+; IHC3+)	IV: QD x1	14% (3 mg/kg) 95% (10 mg/kg)
	STO#395	HER2 pos (FISH+; IHC3+)	IV: QD x1	81% (3 mg/kg) 93% (10 mg/kg)
	STO#151	HER2 pos (FISH+; IHC2+)	IV: Q11D x3	97% (1 mg/kg) 100% (3 mg/kg)
	STO#306	HER2 pos (FISH+; IHC3+)	IV: Q11D x3	86% (1 mg/kg) 99% (3 mg/kg)
	STO#286	HER2 pos (FISH+; IHC3+)	IV: Q11D x3	86% (1 mg/kg) 96% (3 mg/kg)
	STO#091	HER2 pos (FISH+; IHC3+)	IV: Q11D x3	50% (1 mg/kg) 58% (3 mg/kg)
HER2 Low	STO#179	HER2 low (FISH-; IHC1+)	IV: Q11D x3	84% (1 mg/kg) 100% (3 mg/kg)
	STO#345	HER2 low (FISH-; IHC2+)	IV: Q11D x3	34% (1 mg/kg) 59% (3 mg/kg)
	STO#371	HER2 low (FISH-; IHC2+)	IV: Q11D x3	25% (1 mg/kg) 19% (3 mg/kg)
	STO#053	HER2 low (FISH-; IHC2+)	IV: Q11D x3	47% (1 mg/kg) 82% (3 mg/kg)

Activity of ARX788 in HER2 High (STO306) and HER2 Low (STO179) PDX Gastric Cancer Models



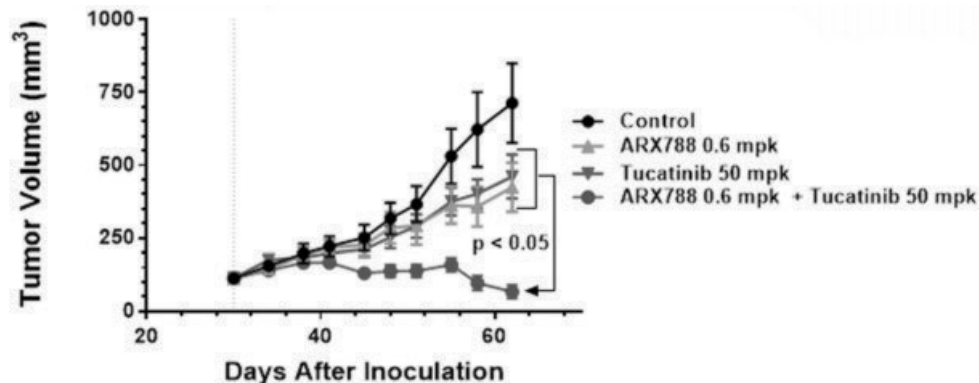
ARX788 was also evaluated for its potential in combination with an anti-PD1 antibody, using the JMT-1 breast cancer model in mice inoculated with human peripheral blood mononuclear cells. In this study, we observed that a low dose of ARX788 had a moderate impact on inhibiting tumor growth and a 3 mg/kg dose of anti-PD1 had no effect, whereas the combination resulted in a sustained complete response beyond four weeks.

Activity of ARX788 and Anti-PD1 Single Agent and Combination in JMT-1 Breast Cancer Model



Further, the activity of ARX788 and a HER2 kinase inhibitor Tukysa (tucatinib) was studied in a BT474 breast cancer xenograft model. This study demonstrated that the combination of ARX788 (0.6 mg/kg, IV, at QW x 6W) and tucatinib (50 mg/kg, po, at QD x 6W) resulted in significantly enhanced tumor growth inhibition (91%) compared to either agent alone when dosed at the same concentration (ARX788 at 0.6 mg/kg, tumor growth inhibition of 41%, tucatinib at 50 mg/kg, tumor growth inhibition of 36%).

The antitumor activity of ARX788 with or without tucatinib in BT474 breast cancer xenograft model



ARX788's preclinical tolerability data indicates a potential improvement over the standard of care. Compared to a conventional cysteine-conjugated HER2 ADC, ARX788 had significantly lower overall toxicity, as indicated by mortality and body weight changes in rats.

Tolerability in Rats for ARX788 and a Conventional Cysteine-Conjugated ADC

Conventional	Cys Conjugate Her2 ADC	Observations	Mortality
	30 mg/kg	Moderate body weight loss, decreased activity, rough haircoat	0/9
	45 mg/kg	Marked body weight loss, decreased activity, rough haircoat, moderate hepatocyte necrosis and hypertrophy	1/9
	60 mg/kg	Marked body weight loss, decreased activity, rough haircoat, moderate hepatocyte necrosis and hypertrophy	3/9
Site-Specific	Ambrx ARX788 ADC	Observations	Mortality
	30 mg/kg	None	0/9
	60 mg/kg	None	0/9
	90 mg/kg	Slight weight loss	0/9

In PK studies across multiple species, we observed ARX788 to be highly stable with overlapping PK profiles for the intact ADC and total antibody. Metabolism studies demonstrated that pAF-AS269 was the sole major metabolite of ARX788, with no evidence for the premature release of free drug often observed in conventional ADCs and responsible for off-target adverse side effects. ARX788 demonstrated a favorable tolerability profile in monkeys, with a highest non-severe lytoxic dose of 10 mg/kg, which was well above the active dose level observed in preclinical tumor models.

Collectively, we believe that these studies support the clinical development of ARX788 in multiple cancers with a broad range of HER2-expression from HER2-high to HER2-low.

ARX305 (CD70 ADC)

ARX305, is an anti-CD70 ADC for the treatment of CD70 over-expressed cancers. CD70 is over-expressed in a broad range of solid and hematologic tumors such as RCC, nasopharyngeal cancers, multiple myeloma, non-Hodgkin's lymphoma and AML.

Our initial development focus for ARX305 is RCC. Approximately 431,000 patients globally were diagnosed with RCC in 2020 and there were 179,000 associated deaths. In 2023, it is estimated that 81,000 new kidney cancer cases will be diagnosed in the United States, 15,000 of whom are estimated to die. Based on U.S. data, the five-year survival rate overall, is 76%, but just 14% if diagnosed with advanced disease. We believe more than half of these patients have tumors that overexpress CD70 to a level that enables targeted therapy with ARX305. Current therapies have relatively low response rates in RCC and there are currently no approved therapies for RCC that target CD70 overexpression.

ARX305 was optimized from our exploratory development of anti-CD70 ADCs with different payloads. The final preclinical candidate of ARX305 employs the same cytotoxic ARX269 payload as used in our other ADC program, ARX788. We have designed ARX305 to address issues observed with earlier generations of ADC technologies through enhanced monoclonal antibody, or mAb, payload stability, which may provide a wider therapeutic window, thereby resulting in greater therapeutic benefit and reduced toxicity compared to conventional ADCs generated using a random conjugation approach.

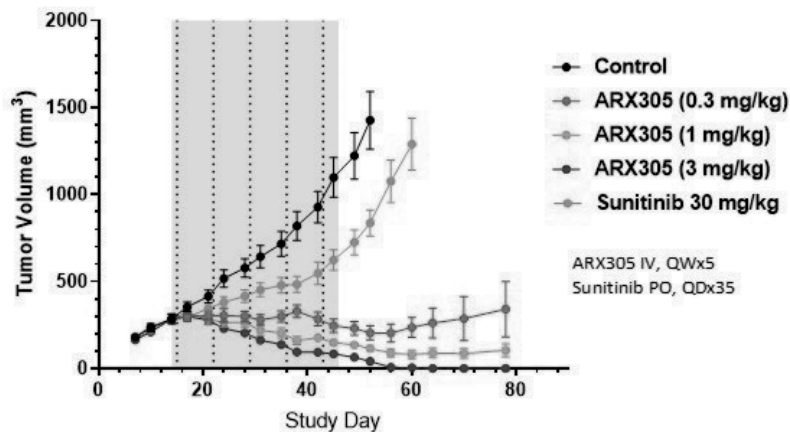
We believe that ARX305 has the potential to be administered at higher dose levels due to mAb-payload stability in plasma, enabling increased efficacy without increased toxicity compared to other anti-CD70 ADCs.

We submitted an IND in January 2022 and received FDA clearance in February 2022. A Phase 1 clinical trial was initiated by NovoCodex in China in the second half of 2022, and we may use data from this trial to inform our own clinical trial involving ARX305. Pending such data and other circumstance, we may seek to initiate a Phase 1a clinical trial in the United States in CD70-positive cancers, including RCC. Should we do so, we will be reimbursed by our partner, NovoCodex for our own internal development costs, up to a certain amount.

Summary of ARX305 Preclinical Studies

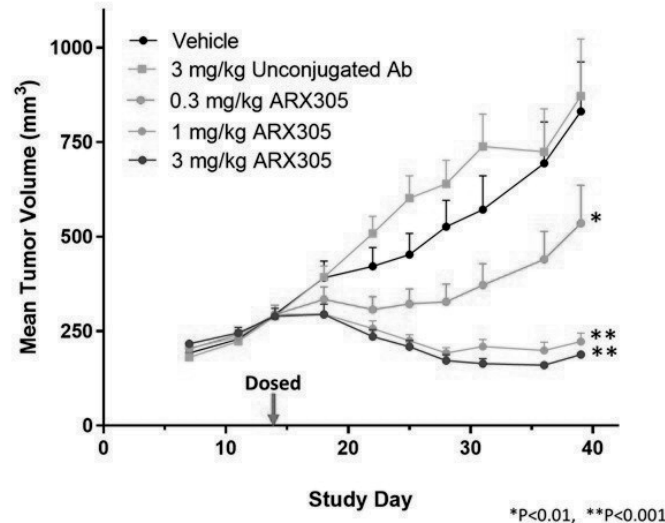
ARX305 has demonstrated robust anti-tumor activity in multiple RCC models. For RCC, ARX305 was evaluated in two cell line-derived xenograft tumor models: 786-OS3 and Caki-1. Single- and multiple-dose regimens of ARX305 resulted in strong anti-tumor activity in the 786-OS3 RCC xenograft model, and outperformed sunitinib, the current standard of care for RCC. Tumor regression was observed at the 3 mg/kg dose of ARX305.

Activity of Multi-Dose of ARX305 in 786-OS3 RCC Xenograft Model



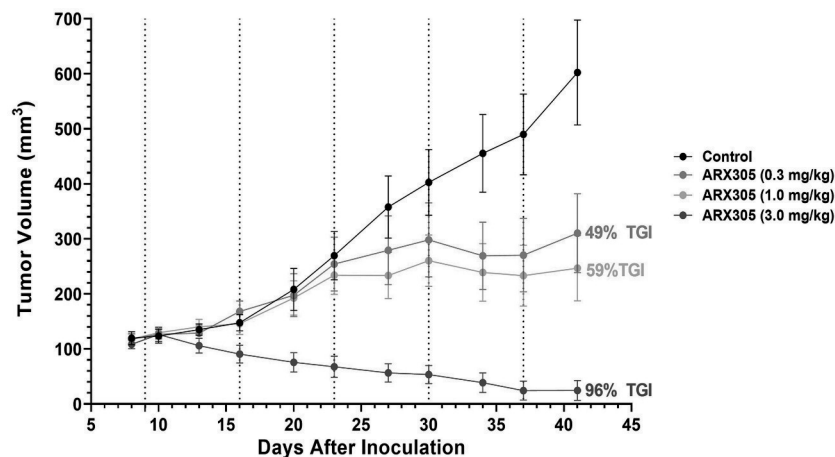
As shown in the figure below, an unconjugated anti-CD70 antibody had no anti-tumor effect in the 786-OS3 RCC model, while a single dose on study day 14 of ARX305 at 0.3, 1, or 3 mg/kg significantly inhibited tumor growth in a dose-dependent manner.

Activity of Single Dose of ARX305 in 786-OS3 RCC Xenograft Model



The potent anti-tumor activity of ARX305 was further demonstrated in another RCC xenograft model (Caki-1). Again, dose-dependent tumor growth inhibition was observed in all three dose levels after weekly dosing for a total of 5 doses.

Activity of Multi-Dose ARX305 in Caki-1 RCC Xenograft Model



ARX305 has also demonstrated activity in other CD70-overexpressing malignancies such as multiple myeloma.

ARX102 (Smart IL-2)

ARX102 is an immuno-oncology IL-2 pathway agonist designed to stimulate the patient's own immune system by targeting the β and γ receptors on the cytotoxic T cell (CD8⁺ effector T cells and natural killer cells) to kill cancer as a single agent or in combination with checkpoint inhibitors.

ARX102 leverages our EBP platform with the goal of addressing the shortcomings of marketed IL-2 therapies. IL-2 has been the focus of several drug development efforts, given its prominence within the human immune system. Approved monotherapies for late-stage melanoma and RCC are associated with potentially severe AEs such as vascular leak syndrome, or VLS, which may limit their adoption. Most of the severe side effects are believed to be mediated by IL-2 binding to the α receptor, which is preferentially expressed in regulatory T cells, or Tregs. The binding of IL-2 to the α receptor stimulates the expansion of Tregs, which leads to suppression of cytotoxic T cell anti-tumor activity. Because β and γ receptors are expressed highly in cytotoxic T cells, IL-2 activity can be engineered toward stimulating cytotoxic T cells preferentially by reducing the alpha receptor binding.

The clinical use of approved IL-2 therapies has also been limited by their extremely short half-life of minutes. Initial efforts to improve half-life focused on increasing stability to reduce dosing frequency. Unfortunately, conventional conjugation methods that improve stability also reduce activity and limit efficacy, safety and convenience.

Our IL-2 targeting molecule was created with the goal of achieving three significant improvements over conventional IL-2 based programs: (1) increased half-life, (2) reduction in unwanted binding to the alpha receptor, and (3) improved potency and functionality. We seek to accomplish this goal by using our site-specific SAA conjugation technology to tune out the alpha receptor binding of IL-2, and using PEGylation to extend half-life, potentially enabling dosing every few weeks. ARX102 is unique as it is produced in our mammalian system, EuCODE. We believe our EuCODE technology enables glycosylation to provide full IL-2 functionality, which may not be achieved with prokaryotic systems such as *E. coli*.

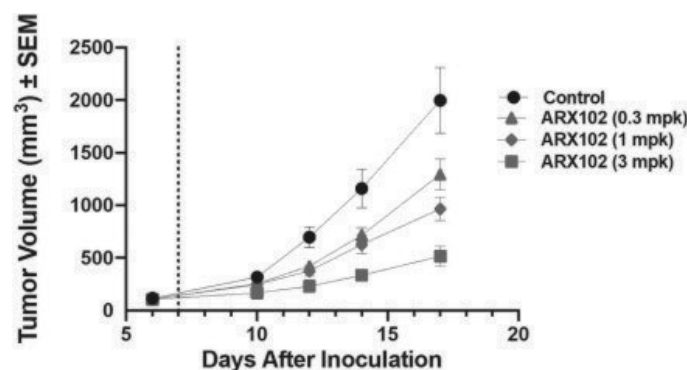
We intend to use data from trials run by Sino Biopharma to inform our own clinical trial involving ARX102.

Summary of ARX102 Preclinical Studies

During the development of ARX102, we tested beta (β) and alpha (α) binding potency of multiple smart IL-2 compounds in *in vitro* experiments.

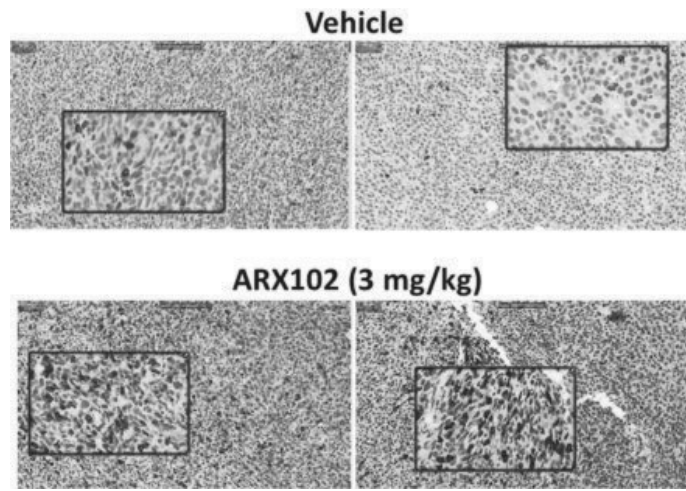
We have engineered multiple versions of our modified IL-2 molecules that preferentially reduce α receptor binding. In the *in vitro* assays, we have identified multiple versions of our IL-2 designs that nearly completely blocked α receptor binding activity. The selected lead candidate, ARX102, was tested for anti-tumor activity in two syngeneic mouse cancer models: CT26 murine colorectal carcinoma and B16 melanoma. As shown in the figures below, ARX102 displayed robust anti-tumor activity with a single dose in the CT26 model.

Dose-response Activity of ARX102 in CT26 Tumor Model



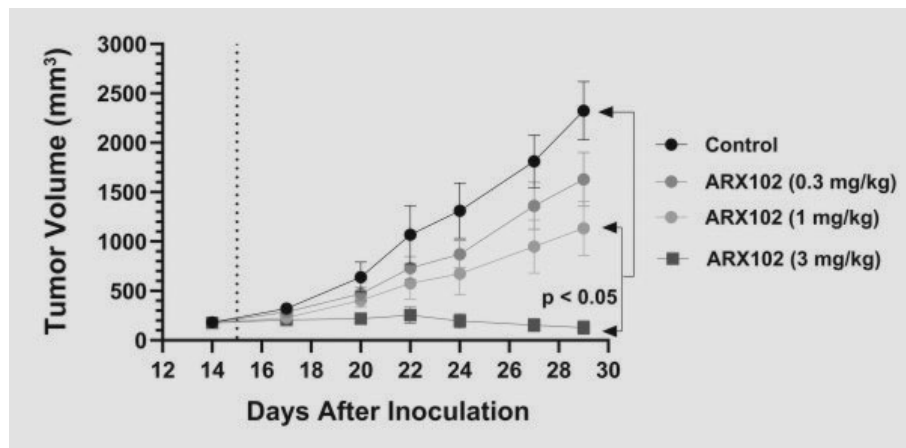
In the same model, ARX102 stimulated a large amount of CD8+ T cell infiltration into the tumor tissue.

ARX102 Increased CD8+ TILs in Tumor Site



Further, ARX102 dosed twice over a two-week period showed robust anti-tumor activity in the E0771 syngeneic breast cancer model, as showed in the figure below.

Antitumor Activity of ARX102 in E0771 Syngeneic Breast Cancer Model



Together with our partner, we are currently conducting IND-enabling studies for ARX102.

Research and Development Agreements

License Agreement with NovoCodex (ARX788)

In June 2013, we entered into a co-development and license agreement with ZMC, which was transferred from ZMC to NovoCodex in March 2019, pursuant to which we granted to NovoCodex an exclusive license to use certain of our patents and know-how to develop, manufacture and sell ARX788 and other HER2 ADC products covered by our intellectual property rights in the People's Republic of China, or PRC. We have retained the rights to develop and commercialize ARX788 and other HER2 ADCs outside of the PRC. However, we have granted to NovoCodex a non-exclusive license for conducting activities in certain other mutually approved jurisdictions, including Australia, to support regulatory approval in the PRC. NovoCodex is responsible, at its sole expense, for making commercially reasonable efforts to develop, obtain regulatory approval for and commercialize the licensed products in China and fund the development of the product in Australia or other jurisdictions approved by a Joint Steering Committee through Phase 1 clinical trials.

In addition, NovoCodex is obligated to transfer all preclinical and clinical data and regulatory filings in certain jurisdictions to us. Should a certain jurisdiction disallow such a transfer, NovoCodex is obligated to grant to us an exclusive, sublicensable right and license in the world, outside of the PRC, under its interest in such information, including regulatory filings and Phase 1 clinical data. We intend to use and rely on this clinical data in our continued development of ARX788.

Under the agreement, we are entitled to receive tiered royalties as high as mid-teens range based on aggregate net sales of ARX788 in the PRC. We will be entitled to receive these royalties until the later of the expiration of the applicable patent rights or 20 years after the first commercial sale of the product in the PRC. In addition, we are obligated to pay NovoCodex royalties in a mid-single digit to low-teens percentage range of any sublicensing profit that we may receive outside of the PRC, depending on what phase of clinical development has been completed at the time of transfer, or a low single digit percentage range on any net sales that we or our successors may receive from sales of ARX788 outside of the PRC, if the market authorization of ARX788 is based on Phase 1 clinical data obtained during our collaboration with NovoCodex.

The agreement terminates upon the later of the expiration of the last-to-expire valid patent claim under the license or 20 years after the first commercial sale of a licensed product in the PRC. NovoCodex may terminate the agreement upon six months' notice to us. Either we or NovoCodex may terminate the agreement upon the other's material breach that remains uncured for 60 days after receipt of notice thereof or insolvency.

License Agreement with NovoCodex (ARX305)

In October 2019, we entered into a co-development and license agreement with NovoCodex, pursuant to which we granted to NovoCodex an exclusive license to develop, have developed, use, manufacture, have manufactured, sell, offer for sale and have sold ARX305 in the PRC.

Pursuant to the agreement, in consideration for the license, NovoCodex granted to us a worldwide, excluding the PRC, exclusive (even to NovoCodex), sub-licensable, royalty-free right and license, to develop, use and exploit any patent or know-how in connection with ARX305 that is developed by NovoCodex alone or jointly between us and NovoCodex. Similarly, NovoCodex granted to us a non-exclusive, sub-licensable, royalty-free right and license to develop, use, and exploit in the PRC any patent or know-how in connection with ARX305 that is developed by NovoCodex.

Upon entry into the agreement, NovoCodex paid us an up-front payment of \$2.0 million. We are eligible to receive up to \$4.0 million in clinical milestones and tiered royalties in the low-teens percentage range of aggregate net sales of ARX305 in China. In the event we transfer or license the Phase 1 clinical data to a third party, NovoCodex is entitled to royalties in a low single-digit to low-teens percentage range on aggregate net sales of ARX305 outside of China, payable by us.

The agreement terminates upon the later of either the expiration of the last-to-expire valid claim of our existing patent rights that would be infringed by the manufacture, license, use or sale of ARX305 or 20 years from the first commercial sale of ARX305. NovoCodex may terminate the agreement upon six months' prior written notice. Either party may terminate the agreement upon a material breach by the other party. If NovoCodex terminates the agreement at will or we terminate the agreement due to a material breach by NovoCodex, the exclusive license granted to NovoCodex by us will revert to us and we would have the right to develop, use, manufacture and sell ARX305 in the PRC. Upon NovoCodex's termination of the agreement upon six months' notice to us, the exclusive license granted to NovoCodex by us will revert to us.

License Agreement with The Regents of the University of California

In December 2009, we entered into an exclusive license agreement with The Regents of the University of California, or The Regents, pursuant to which we were granted an exclusive license to a patent portfolio containing five issued U.S. patents, one pending U.S. patent application and 12 foreign patents and patent applications owned by The Regents that cover the inventions of copper-free click chemistries. The Regents also granted us the right to sublicense the patent portfolio to our affiliates. We are obligated to pay to The Regents a low-single-digit percentage range of any up-front cash or consideration received for the sublicensed rights in addition to any royalties.

In consideration for the license rights, we paid an upfront fee of \$0.2 million to The Regents and are obligated to pay an annual license maintenance fee of \$20,000 unless we are paying royalties to The Regents. We are required to pay The Regents, on a product-by-product basis, up to an aggregate of \$2.4 million upon the first achievement of certain clinical and regulatory milestones for any licensed product.

We will owe royalties to The Regents in the amount of a low-single-digit percentage range of net sales of licensed products upon the earlier of the agreement's termination, the expiration of the last to expire valid claim of the licensed patents or a licensed patent being deemed invalid by a court of competent jurisdiction and last resort. Additionally, we will owe payments in the low seven figures in the aggregate to The Regents upon the achievement of certain milestones set forth in the agreement.

We may terminate the agreement at any time, in whole or in part, upon 90 days prior notice. The Regents may terminate the agreement upon breach by us which is not cured within 60 days of receipt of notice of such breach. Unless otherwise terminated by us or The Regents, the agreement will terminate upon the expiration of the last to expire patent or abandonment of the last to be abandoned patent application licensed under the agreement. For patents directed to the ReCODE system, the last Regents patent expired in 2022. Accordingly, under the license agreement, our royalty obligations for patents directed to the ReCODE system ended in 2022. For patents directed to the EuCODE system, the last Regents patent is expected to expire in 2024. Accordingly, under the license agreement, our royalty obligations for patents directed to the EuCODE system end in 2024.

License Agreements with TSRI and Calibr

In August 2003, we entered into a license agreement, or as amended, the TSRI Agreement, with TSRI, pursuant to which TSRI granted us an exclusive, sublicensable, worldwide license for the use, sale, and importation of certain products, processes, services, biological materials and technology arising out of designated patent rights related to the *in vivo* incorporation of amino acids, protein arrays and glycoprotein synthesis, among others. Through this exclusive license, we currently have exclusive rights to approximately 19 issued U.S. patents and 61 foreign patents relating to methods and reagents for making proteins containing non-natively encoded amino acids. Any patent within this portfolio that has been issued or may issue in the future will expire between 2023 and 2026. We and TSRI are entitled to a share of any future licensing income generated from this program. We are required to provide TSRI with written annual reports on our product development progress or efforts to commercialize product candidates derived from the licensed rights. We are obligated to use commercially reasonable efforts to commercialize products under the TSRI agreement.

In addition, we have agreed to pay TSRI royalties on net sales of licensed products, processes and services on a country-by-country basis. These royalties are in the low-single-digit percentage range of annual net sales. We are also obligated to pay to TSRI earned royalties on sublicensing revenues, on a country-by-country basis, in the mid-single-digit percentages. All royalty obligations are subject to adjustment for combination products.

The TSRI Agreement terminates upon the expiration of our royalty obligations to TSRI. Our royalty obligations terminate on a country-by-country basis for licensed products, processes and services upon the expiration of the last to expire of a valid claim within the applicable patent rights that cover the product, process, or service, or, if no such patent rights exist but such product, process, or service utilizes or incorporates a licensed biological material, then our royalty obligations terminate 15 years after the date of the first commercial sale of the licensed product, process or service. Our royalty obligations for licensed biological materials terminate 15 years after the date of the first commercial sale. We can terminate the TSRI Agreement upon 90 days' written notice to TSRI. TSRI may terminate the TSRI Agreement for certain enumerated breaches of our obligations that are not cured within a specified period after receiving written notice.

In August 2013, we entered into a collaborative license agreement, or as amended, the Calibr Agreement, with the California Institute for Biomedical Research, or Calibr, which later merged with TSRI, pursuant to which we granted Calibr a non-exclusive research license to certain of our patents, know-how and materials, and Calibr granted us a perpetual, irrevocable, worldwide, non-exclusive license, for internal research purposes only, to certain inventions, patents and technology controlled by Calibr and associated with a research plan approved by a joint steering committee. In addition, Calibr granted us an exclusive option to acquire a perpetual, irrevocable, worldwide license to certain potential inventions, patents and other intellectual property associated with a research plan approved by a joint steering committee. The collaboration focuses on projects related to novel molecular targets, polypeptide conjugates and enabling technologies.

Pursuant to the Calibr Agreement, Calibr secured a license to CCW702, a bispecific targeting prostate cancer cells. Calibr licensed the global rights to develop CCW702, and subsequently licensed the program to AbbVie in an option agreement. We are eligible to receive a portion of any sublicensing income that Calibr may receive from licensing the product candidate.

In consideration of the license granted to us, we paid Calibr an upfront fee of approximately \$0.3 million. We have also paid Calibr \$3.3 million in consideration for Calibr's research activities undertaken to advance the collaboration and will owe Calibr a portion of any sublicensing fees that we may receive from licensing any patents or product candidates. We will also owe Calibr royalties on a product-by-product and country-by-country basis in the low single-digit percentages. The royalty obligations continue until the earlier of the last to expire valid claim of the licensed patents that would be infringed by the sale of the licensed product in such country or ten years after the first commercial sale of the licensed product in the country.

The Calibr Agreement terminates upon the expiration of the royalty term. Either party may terminate the Calibr Agreement for any payment default or other material breach by the other party that is not cured within 60 days after receiving written notice. Calibr may terminate the agreement upon specified change of control events with respect to us.

Competition

The biotechnology and pharmaceutical industries are highly competitive and dynamic, characterized by continuing and rapid technological advancement. Our technology platforms, product candidates, know-how, experience and scientific resources will face competition from major pharmaceutical and biotechnology companies, academic institutions, governmental agencies and public and private research institutions, among others. Any product candidates that we successfully develop and commercialize will compete with existing therapies and new therapies that may become available in the future. Key product features that would affect our ability to effectively compete with other therapeutics include the efficacy, safety and convenience of our products. The level of generic competition and the availability of reimbursement from the government and other third-party payers will also significantly impact the pricing and competitiveness of our products. Our commercial potential could be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, are more convenient or are less expensive than products that we may develop. Our competitors also may obtain FDA or other regulatory body approval for their products more rapidly than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market or make our development more complicated.

We compete with other companies working to develop immunotherapies and targeted therapies for the treatment of cancer including divisions of large pharmaceutical and biotechnology companies of various sizes. These companies are developing therapies of many different modalities including small molecules, monoclonal antibodies, ADCs, bispecific antibodies and cell therapies. Many of the companies against which we may compete have significantly greater financial resources and expertise than we do in research and development, manufacturing, preclinical and clinical testing, obtaining regulatory approvals and marketing approved products. Smaller or early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These competitors also compete with us in recruiting and retaining qualified scientific and management personnel and establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs.

If ARX788, our most advanced product candidate, is approved, it will compete with a range of existing cancer therapies, including two currently marketed ADCs targeting HER2-positive cancers, Kadcyla and Enhertu. Additionally, there are multiple clinical and preclinical programs, including biologics and small molecules, in development for HER2-positive cancers. Without the results from clinical trials, it is difficult to assess whether our product candidates will have the appropriate therapeutic index to provide a meaningful therapy for these various cancers and the extent to which they can successfully compete against current and future standard of care therapies. With respect to our other indications, the clinical development pipeline includes many programs at various stages of development and this competitive landscape will continue to evolve as we advance our programs through clinical trials.

Further, there are many companies pursuing a variety of approaches to protein conjugations and modifications. Multiple companies, including larger and more-established companies, are pursuing traditional approaches that rely upon natural amino acids, usually a cysteine or lysine, as a conjugation site. Another approach looks to modify the sugar residues of naturally occurring amino acids. Our approach is to encode a non-natural amino acid at optimized positions within the proteins, and Sutro Biopharma, Inc. (Sutro Biopharma), Synthorx Inc. and other early-stage companies also use this approach. Other companies using antibody-drug conjugates to target innate immune receptors include Actym Therapeutics, Mersana Therapeutics and Takeda Pharmaceuticals. Immunotherapy and validated pathway approaches are further being pursued by many smaller biotechnology companies as well as larger pharmaceutical companies. We also face competition from validated pathway therapy treatments offered by companies such as AstraZeneca, Byondis, Daiichi Sankyo, Genentech, MacroGenics, Pieris Pharmaceuticals, Puma, Seattle Genetics, Spectrum Pharmaceuticals and Zymeworks. We also face competition from companies that continue to invest in innovation in the antibody-drug conjugate field, including but not limited to AbbVie, ADC Therapeutics, Astellas Pharma, BioAtla, Celldex Therapeutics, CytomX Therapeutics, Eli Lilly and Company, GlaxoSmithKline, Genmab, ImmunoGen, Immunomedics, Millennium Pharmaceuticals, MorphoSys AG, Novartis, Pfizer, Sanofi, Seattle Genetics, Sutro Biopharma and VelosBio. There are various factors that differentiate us from these competitors such as our bacterial systems, but without the results from our clinical trials, it is difficult to assess whether our approach provides potential safety and efficacy benefits versus other approaches. Specifically, the partnership between AstraZeneca and Daiichi Sankyo, has accelerated the expansion of the clinical development program for Daiichi Sankyo's Enhertu, a HER2 ADC, with now almost 50 ongoing clinical trials in a broad range of cancer types and cancer stages. The scope and resources being dedicated to the Enhertu program may negatively impact our planned clinical trials and development for ARX788, including as a result of challenges in patient enrollment due to the lack of patients or as a result of their ability to complete clinical trials or obtain approvals more rapidly than us. For example, in September 2021, Daiichi Sankyo released the results for its Destiny-Breast03 clinical trial, studying the activity of Enhertu compared to Kadcyla in second line metastatic breast cancer. With statistically significant and clinically meaningful improvement in the primary endpoint PFS over Kadcyla, both NCCN and ESMO soon revised the HER2-positive metastatic breast cancer treatment guideline to displace Kadcyla with Enhertu as the new standard of care in second line HER2-positive breast cancer.

Manufacturing

We do not own or operate nor currently have plans to establish any manufacturing facilities. We rely on, and expect to continue to rely on third parties for the manufacture of our product candidates for preclinical and clinical testing, as well as for commercial manufacturing if any of our product candidates obtain marketing approval. We believe that we currently have sufficient supply to carry out our ongoing and planned trials, but there is a risk that we may run out of supply due to factors beyond our control. We also rely on, and expect to continue to rely on third parties to package, label, store and distribute our investigational product candidates, as well as our commercial products if marketing approval is obtained. We believe that this strategy allows us to maintain a more efficient infrastructure by eliminating the need for us to invest in our own manufacturing facilities, equipment and personnel, while also enabling us to focus our expertise and resources on the development of our product candidates.

We utilize both mammalian, or EuCODE, and bacterial, or ReCODE, expression platforms employing standard manufacturing equipment and facilities. We have analytical and process development capabilities and can manufacture non-cGMP material in our own facility. We generally perform cell line, analytical and process development for our product candidates internally and manufacture the drug necessary to conduct non-GLP preclinical studies of our investigational product candidates. We occasionally outsource the production of research and development material. We do not have, and we do not currently plan to, acquire or develop the facilities or capabilities to manufacture bulk drug substance or filled drug product for use in human clinical trials. We rely on third-party manufacturers to produce the bulk drug substances required for our clinical trials and expect to continue to rely on third parties to manufacture and test clinical trial drug supplies for the foreseeable future. With a partner, we have successfully scaled bacterial fermentation of a ReCODE product to the commercial-scale of 50,000 liters in 2014, and we scaled our EuCODE platform to 2,000 liters in 2015. To date, we have successfully manufactured multiple batches of monoclonal antibodies at 2000-L scale based on the EuCODE platform with overall yield of at least 65%. We have successfully manufactured ARX788 with an optimized process and a new dosage form, a more commercially viable lyophilized powder formulation, and demonstrated analytical comparability with pre-change clinical trial materials. The ARX788 drug product batch size is approximately 9,500 vials. We also contract with additional third parties for the filling, labeling, packaging, testing, storage and distribution of our investigational drug products. We employ personnel with the significant scientific, technical, production, quality and project management experience required to oversee our network of third-party suppliers and to manage manufacturing, quality data and information for regulatory compliance purposes.

Our contract suppliers manufacture drug substance and drug product for clinical trial use in compliance with cGMP and applicable local regulations. cGMP regulations include requirements relating to the organization of personnel, buildings and facilities; equipment; control of components and drug product containers and closures; production and process controls; packaging and labeling controls; holding and distribution; laboratory controls; records and reports; and returned or salvaged product. The manufacturing facilities for our products must meet cGMP requirements and FDA satisfaction before any product is approved. We ensure cGMP compliance of our suppliers through regular quality inspections performed by our Quality Assurance group. Our third-party manufacturers are also subject to periodic inspections of facilities by the FDA and other regulatory authorities, including reviews of procedures and operations used in the testing and manufacture of our products, to assess our compliance with applicable regulations. Failure to comply with statutory and regulatory requirements subjects a manufacturer to possible legal or regulatory action, including warning letters, the seizure or recall of products, injunctions, consent decrees placing significant restrictions on or suspending manufacturing operations and civil and criminal penalties. These actions could have a material adverse impact on the availability of our products. In addition, contract manufacturers often encounter difficulties involving production yields, quality control and quality assurance, as well as shortages of qualified personnel.

Commercialization

We intend to retain significant development and commercial rights to our product candidates and, if marketing approval is obtained, to commercialize our product candidates on our own, or potentially with a partner, in the United States and other regions. We currently have no sales, marketing or commercial product distribution capabilities. We intend to build the necessary infrastructure and capabilities over time for the United States, and potentially other regions, following further advancement of our product candidates. Clinical data, the size of the addressable patient population, and the size of the commercial infrastructure and manufacturing needs may all influence or alter our commercialization plans.

Intellectual Property

We strive to protect our product candidates and our technology platforms through a variety of methods. In regards to our product candidates, we seek and maintain patents intended to cover our products and compositions, their methods of use for treating diseases, the processes for their manufacture, and, as our product candidates proceed through clinical studies, the innovations that arise from these efforts. As a result, we constantly seek to obtain domestic and international patent protection and endeavor to promptly file patent applications for new commercially valuable inventions to expand our intellectual property portfolio. In addition, we have entered into exclusive license agreements with various academic and research institutions to obtain certain rights that permit us to develop and commercialize our product candidates. Finally, we also rely on trade secrets, know-how, continuing technological innovation and in-licensing opportunities to develop and maintain our proprietary position with our technology platform.

More specifically, we first seek patent protection for our product candidates with claims that are directed to the novel ADCs and IOCs that have incorporated our non-natural amino acids as well as claims directed to the use of these novel ADCs and IOCs for the treatment of diseases. We also seek patent protection on the novel methods we use to make and manufacture these novel ADCs and IOCs. As our novel ADCs and IOCs proceed through pre-clinical and clinical development, we constantly strive to identify new innovations, and, as appropriate, file for additional patent protection.

In regards to our technology platforms, we rely on a combination of patent protection and trade secret protection. Initially, we primarily relied on patent protection for the platform innovations that were developed at TSRI, and then in-licensed to Ambrx, as well as on patent protection for the platform innovations developed at Ambrx. Subsequently, we have primarily relied on protecting the substantial know-how that has arisen from more than 15 years of manufacturing and process development at Ambrx as a trade secret. However, if appropriate, we will continue to seek opportunities to protect our technology platform with patent protection.

We believe that we have a significant global intellectual property position and substantial know-how relating to our product candidate and the incorporation of non-natively encoded amino acids into proteins.

We continually assess and refine our intellectual property strategy as we develop new product candidates and platform technologies. To that end, we are prepared to file additional patent and trademark applications if our intellectual property strategy requires such filings or where we seek to adapt to competition or seize business opportunities. Further, we are prepared to file patent and trademark applications, as we consider appropriate under the circumstances, relating to the new technologies that we develop.

In addition to filing and prosecuting patent applications in the United States, we also file patent applications pursuant to the Patent Cooperation Treaty, or PCT, in additional countries where we believe such foreign filing is likely to be beneficial, including Australia, Brazil, Canada, China, Europe, Hong Kong, India, Israel, Japan, Mexico, Singapore, and South Korea. We may also file trademark applications in additional countries pursuant to the Paris Convention claiming priority from our U.S. trademark applications where they are likely to be beneficial, and we also intend to file applications for trademark registrations in connection with our product candidates in various jurisdictions, including the United States.

Intellectual Property Relating to Our HER2 (ARX788) Product Candidate

With regard to our HER2 ADC product candidate, as of December 31, 2022, we solely own three issued U.S. patents and one pending U.S. patent application and have approximately 70 issued patents and 12 patent applications pending in various countries, including Australia, Canada, China, Europe, India, Israel, Japan, Mexico and South Korea. These applications relate to the composition of matter and methods for making HER2 ADC. Any patents that issue from these applications will expire around 2032, excluding any available extension of the patent term. The issued patents provide patent protection until around 2033 in the United States and around 2032 in other countries, excluding any available extension of the patent term.

We also have a solely owned second application protecting our HER2 ADC product candidate that includes one pending PCT application. Any patents that issue from this application will expire around 2042, excluding any available extension of the patent term.

Intellectual Property Relating to Our PSMA (ARX517) Product Candidate

With regard to our PSMA ADC product candidate, as of December 31, 2022, we solely own one issued U.S. patent and one pending U.S. patent application and have approximately 27 issued patents and six patent applications pending in various countries and regions, including Australia, Canada, China, Europe, India, Israel, Japan, Mexico and South Korea. These applications relate to the composition of matter and methods for making PSMA ADC. Any patents that issue from these applications will expire around 2033, excluding any available extension of the patent term.

We also have a solely owned second application protecting our PSMA ADC product candidate that includes one pending U.S. patent application and approximately 13 patent applications pending in various countries, as of December 31, 2022, including Australia, Canada, China, Europe, India, Israel, Japan, Mexico, and South Korea. Any patents that issue from these applications will expire around 2039, excluding any available extension of the patent term.

Intellectual Property Relating to Our CD70 Product Candidate

With regard to our CD70 ADC product candidate, as of December 31, 2022, we own two issued U.S. patents and one pending U.S. patent application and have approximately 22 issued patents and ten patent applications pending in various countries and regions, including Australia, Canada, China, Europe, India, Israel, Japan, Mexico and South Korea. These applications relate to the composition of matter and methods for making CD70 ADC. Any patents that issue from these applications will expire around 2033, excluding any available extension of the patent term.

Intellectual Property Relating to Our IL-2 Product Candidate

Regarding our IL-2 I/O product candidate, we own one pending U.S. patent application and have approximately 14 patent applications pending in various countries and regions, including Australia, Canada, China, Europe, India, Israel, Japan, Mexico and South Korea. These applications relate to the composition of matter, including PEGylated IL-2 compositions, formulations, methods of manufacturing, and methods of treating diseases, including cancers. China rights to the product candidate are currently controlled by our partner Sino Biopharma. Any patents that issue from these will expire around 2039, excluding any available extension of the patent term.

We also own a second application protecting our IL-2 product candidate that currently includes one pending U.S. patent application and approximately ten patent applications pending in various countries and regions, including Australia, Canada, China, Europe, India, Israel, Japan, Mexico and South Korea. These applications relate to the composition of matter, including PEGylated IL-2 compositions, formulations, methods of manufacturing, and methods of treating diseases, including cancers. China rights to the product candidate are currently controlled by our partner Sino Biopharma. Any patents that issue from these applications will expire around 2041, excluding any available extension of the patent term.

Intellectual Property Relating to Our TLR Agonists Product Candidate

With regards to our TLR7/8 agonist product candidate, we solely own one pending U.S. patent application and have approximately 14 patent applications pending in various countries and regions as of December 31, 2022, including Australia, Canada, China, Europe, India, Israel, Japan, Mexico, and South Korea. These applications relate to the composition of matter of our ISACs, formulations, methods of manufacturing, and methods of treating diseases, including cancers. Any patents that issue from these applications will expire around 2040, excluding any available extension of the patent term.

We also have a solely owned second application protecting our TLR7/8 agonist product candidate that currently includes one pending PCT patent application and one Taiwanese patent application as of December 31, 2022. These applications relate to the composition of matter, including PEGylated TLR7/8 compositions, formulations, methods of manufacturing, and methods of treating diseases, including cancers. Any patents that issue from these applications will expire around 2041, excluding any available extension of the patent term.

Intellectual Property Relating to Our CD3Folate (Bispecific) Product Candidate

With regards to our CD3-Folate bispecific product candidate, as of December 31, 2022, we have one issued patent, one pending U.S. patent application and approximately 14 patent applications pending in various countries and regions as of December 31, 2022, including Australia, Canada, China, Europe, India, Israel, Japan, Mexico, and South Korea. These applications relate to the composition of matter, formulations, methods of manufacturing, and methods of treating diseases, including cancers. China rights to the product candidate are currently out-licensed to our partner Sino Biopharma. Any patents that issue from these applications will expire around 2036, excluding any available extension of the patent term.

We also own a second application protecting our CD3-Folate bispecific product candidate that currently includes one pending U.S. patent application and approximately 13 patent applications pending in various countries and regions as of December 31, 2022, including Australia, Canada, China, Europe, India, Israel, Japan, Mexico and South Korea. These applications relate to the composition of matter, including CD3-Folate bispecific composition of matter, formulations, methods of manufacturing, and methods of treating diseases, including cancers. China rights to the product candidate are currently out-licensed to our partner Sino Biopharma. Any patents that issue from these applications will expire around 2039, excluding any available extension of the patent term.

Intellectual Property Relating to Our EuCODE and ReCODE Platforms

We own 12 families of U.S. and foreign patents and patent applications covering our EuCODE and ReCODE platforms as of December 31, 2022. These families include 25 issued U.S. patents relating to key components of our EuCODE and ReCODE platforms and methods of manufacturing the polypeptides that contain a non-natively encoded amino acid. Our patent applications contain claims covering orthogonal tRNA synthetases, or RSs; orthogonal tRNA's; cells that contain the orthogonal RS and tRNA; and methods for manufacturing polypeptides comprising a non-natively encoded amino acid. Our patent applications also have claims directed at protecting our linkers, payloads, unconjugated and conjugated compounds, including click chemistry and oxime chemistry conjugates. The issued U.S. patents and any U.S. patents issuing from our pending U.S. patent applications will expire between 2024 and 2031. For our ReCODE platform, we own issued foreign patents in Australia, Canada, China, Europe, Hong Kong, India, Israel, Japan, Mexico, New Zealand, Singapore, and South Korea. For our EuCODE platform, we own issued foreign patents in Australia, Canada, China, Europe, Hong Kong, India, Israel, Japan, Mexico, New Zealand, and Singapore.

Moreover, even if the patents that will issue from our pending U.S. applications are to expire after 2031, we believe we have appropriately protected our EuCODE and ReCODE platforms with the substantial body of trade secrets and know-how that we have developed over the last 15 years of research at Ambrx.

Our EuCODE mammalian platform is utilized to generate most of our ADC bioconjugates. Our solely owned patent estate as of December 31, 2022, includes 3 issued U.S. patents and approximately 63 issued foreign patents with claims directed to an orthogonal tRNA for vertebrate cells that mediates the incorporation of non-natively encoded amino acids into an expressed protein, methods of manufacturing in a vertebrate cell a protein comprising non-natively encoded amino acids using an orthogonal aminoacyl tRNA synthetase that preferentially aminoacylates the orthogonal tRNA with the non-natively encoded amino acid, and suppressor tRNA transcription in vertebrate cells.

In addition, our EuCODE mammalian platform is protected by a body of trade secrets that is based on more than 15 years of research and development at Ambrx. We believe that these trade secrets have provided, and will continue to provide, us with a competitive edge for developing and then manufacturing our product candidates well after our patents have expired.

With regard to our ReCODE bacterial platform, we also have an exclusive license to a patent portfolio containing three families of U.S. and foreign patents and patent applications co-owned by TSRI and The Regents. Through this exclusive license, we have exclusive rights to approximately 19 issued U.S. patents, and 61 issued foreign patents relating to methods and reagents for making proteins containing non-natively encoded amino acids as of December 31, 2022. Any patent within this portfolio that has been issued or may issue in the future will expire between 2023 and 2026.

Our EuCODE patent estate also includes applications with claims directed to our ADC product candidates anti-HER2, anti-PSMA and anti-CD70 ADCs; claims directed to our IOC product candidates IL-2, and TLR7/8 agonists; claims directed to our platform technology for future products and developments.

The ability to obtain patent protection and the degree of such protection depends on a number of factors, including the extent of the prior art, the novelty and non-obviousness of the invention, and the ability to satisfy the enablement requirement of the patent laws. In addition, for each of our patent applications, claiming strategy is determined on a case-by-case basis, taking into consideration existing patent office rules and regulations, advice of our counsel in each jurisdiction, and our business model. We cannot be sure that patents will be granted with respect to any of our pending patent applications or with respect to any patent applications we may own or license in the future, nor can we be sure that any of our existing patents or any patents we may own or license in the future will be useful in protecting our technology.

The term of individual patents depends upon the laws of the countries in which they are obtained. In most countries in which we file, the patent term is 20 years from the earliest date of filing of a non-provisional patent application. However, the term of U.S. patents may be extended for delays incurred due to compliance with the FDA requirements or by delays encountered during prosecution that are caused by the USPTO. For example, for drugs that are regulated by the FDA under the Hatch-Waxman Act, it is permitted to extend the term of a patent that covers such a drug for up to five years beyond the normal expiration date of the patent. In the future, if and when our biopharmaceutical product candidates receive FDA approval, we expect to apply for patent term extensions on patents covering those product candidates. We intend to seek patent term extensions to any of our issued patents in any jurisdiction where these are available; however, there is no guarantee that the applicable authorities, including the USPTO and FDA, will agree with our assessment of whether such extensions should be granted, and even if granted, the length of such extensions.

The actual protection afforded by a patent varies on a product-by-product basis, from country-to-country, and depends upon many factors, including the type of patent, the scope of its coverage, the availability of regulatory-related extensions, the availability of legal remedies in a particular country and the validity and enforceability of the patent. The patent positions of companies like ours are generally uncertain and involve complex legal and factual questions. No consistent policy regarding the scope of claims allowable in patents in the field of antibody drug conjugates has emerged in the United States. The patent situation outside of the United States is even more uncertain. Changes in the patent laws and rules, either by legislation, judicial decisions, or regulatory interpretation in the United States and other countries, may diminish our ability to protect our inventions and enforce our intellectual property rights, and more generally could affect the value of our intellectual property. In particular, our ability to stop third parties from making, using, selling, offering to sell, importing, or otherwise commercializing any of our patented inventions, either directly or indirectly, will depend in part on our success in obtaining, defending,

and enforcing patent claims that cover our technology, inventions, and improvements. With respect to both licensed and company-owned intellectual property, we cannot be sure that patents will be granted with respect to any of our pending patent applications or with respect to any patent applications filed by us in the future, nor can we be sure that any of our existing patents or any patents that may be granted to us in the future will be commercially useful in protecting our platform, product candidates, or the methods used to manufacture them. Moreover, our issued patents and those that may issue in the future may not guarantee us the right to practice our technology in relation to the commercialization of our platform's product candidates. The area of patent and other intellectual property rights in biotechnology is an evolving one with many risks and uncertainties, and third parties may have blocking patents that could be used to prevent us from practicing our proprietary technology and commercializing our EuCODE and ReCODE technology platforms and product candidates. Our issued patents and those that may issue in the future may be challenged, narrowed, circumvented, or invalidated, which could limit our ability to stop competitors from marketing related platforms or product candidates or limit the length of the term of patent protection that we may have for our ADC and IOC product candidates. In addition, the rights granted under any issued patents may not provide us with protection or competitive advantages against competitors with similar technology. Furthermore, our competitors may independently develop similar technologies. For these reasons, we may have competition for our ADC and IOC product candidates. Moreover, because of the extensive time required for development, testing and regulatory review of a potential product, it is possible that before any product candidate can be commercialized, any related patent may expire or remain in force for only a short period following commercialization, thereby reducing any advantage of the patent for this and other risks related to our proprietary technology, inventions, improvements, platforms and product candidates. Please see "*Risk Factors—Risks Related to Our Intellectual Property*" for additional information on the risks associated with our intellectual property strategy and portfolio.

Government Regulation

Government authorities in the United States at the federal, state and local level and in other countries and jurisdictions, including the PRC, extensively regulate, among other things, the research, development, testing, manufacture, quality control, approval, safety, efficacy, labeling, packaging, storage, record-keeping, promotion, advertising, distribution, post-approval monitoring and reporting, marketing and export and import of drug and biological products. Generally, before a new drug or biologic can be marketed, considerable data demonstrating its quality, safety and efficacy must be obtained, organized into a format specific for each regulatory authority, submitted for review and approved by the regulatory authority.

Regulatory Approval of Biologics in the United States

In the United States, biological products used for the prevention, treatment or cure of a disease or condition of a human being, such as our product candidates, are subject to regulation under the Federal Food, Drug, and Cosmetic Act, or the FDCA, and the Public Health Service Act, or the PHSA, their implementing regulations, and other federal, state, and local regulations that govern, among other things, the research, development, testing, manufacture, quality control, approval, safety, efficacy, labeling, packaging, storage, record-keeping, promotion, advertising, distribution, import and export, post-approval monitoring and reporting, and marketing of biological products. The process of obtaining regulatory approvals and the subsequent compliance with appropriate federal, state, local and foreign statutes and regulations require the expenditure of substantial time and financial resources. Failure to comply with applicable United States requirements may subject a company to a variety of administrative or judicial sanctions, such as clinical hold, FDA refusal to approve pending BLAs, warning or untitled letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, civil penalties and criminal prosecution.

Further, even if we obtain the required regulatory approvals for our product candidates, pharmaceutical companies are subject to myriad federal, state, and foreign healthcare laws, rules, and regulations governing all aspects of our operations, including, but not limited to, our relationships with healthcare professionals, healthcare institutions, distributors of our products, and sales and marketing personnel; governmental and other third-party payor coverage and reimbursement of our products; and data privacy and security. Such laws, rules, and regulations are complex, continuously evolving, and, in many cases, have not been subject to extensive interpretation by applicable regulatory agencies or the courts. We are required to invest significant time and financial resources in policies, procedures, processes, and systems to ensure compliance with these laws, rules, and regulations, and our failure to do so may result in the imposition of substantial monetary or other penalties by federal or state regulatory agencies. Our product candidates and any future product candidates must be approved by the FDA pursuant to a BLA before they may be legally marketed in the United States. The process generally involves the following:

- completion of extensive preclinical laboratory tests and animal studies in accordance with applicable regulations, including studies conducted in accordance with good laboratory practice, or GLP, requirements;
- submission to the FDA of an IND, which must become effective before human clinical trials may begin;
- approval of the protocol and related documentation by an institutional review board, or IRB, or independent ethics committee at each clinical trial site before each clinical trial may be commenced;
- performance of adequate and well-controlled human clinical trials in accordance with applicable FDA regulations, including good clinical practice, or GCP, requirements and any other clinical trial-related regulations for the protection of human research subjects and their health information and to establish the safety and efficacy of the investigational product for each proposed indication;
- preparation and submission to the FDA of a BLA for marketing approval that includes sufficient evidence of establishing the safety, purity, and potency of the proposed biological product for its intended indication, including from results of preclinical testing and clinical trials;
- payment of any user fees for FDA review of the BLA;
- a determination by the FDA within 60 days of its receipt of a BLA to accept the filing for review;
- satisfactory completion of one or more FDA pre-approval inspections of the manufacturing facility or facilities where the biological product, or components thereof, will be produced to assess compliance with current good manufacturing practice, or cGMP, requirements to assure that the facilities, methods and controls are adequate to preserve the biological product's identity, strength, quality and purity;
- satisfactory completion of any potential FDA audits of the clinical trial sites that generated the data in support of the BLA to assure compliance with GCP requirements and integrity of the clinical data;
- FDA review and approval of the BLA, including consideration of the views of any FDA advisory committee, where appropriate and if applicable; and
- compliance with any post-approval requirements, including a risk evaluation and mitigation strategy, or REMS plan, where applicable, and post-approval studies required by the FDA as a condition of approval.

Preclinical Studies

Before testing any biological product candidates in humans, the product candidate must undergo rigorous preclinical testing. Preclinical studies include laboratory evaluation of the product candidate's biological characteristics, chemistry, toxicity and formulation, as well as *in vitro* and animal studies to assess the potential safety and activity of the product candidate. The conduct of preclinical studies is subject to federal regulations and requirements, including GLP regulations for safety/toxicology studies.

Prior to commencing an initial clinical trial in humans with a product candidate in the United States, an IND must be submitted to the FDA and the FDA must allow the IND to proceed. An IND is a request for authorization from the FDA to administer an investigational product to humans and must become effective before human clinical trials may begin. Some long-term preclinical testing may continue after the IND is submitted. In support of a request for an IND, applicants must submit the results of the preclinical tests, together with manufacturing information, analytical data, any available clinical data or literature and plans for clinical trials, among other things, to the FDA as part of an IND. An IND automatically becomes effective 30 days after receipt by the FDA, unless before that time the FDA raises safety concerns or questions related to one or more proposed clinical trials and places the trial on clinical hold. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. As a result, submission of an IND may or may not result in the FDA authorizing clinical trials to commence.

Clinical Trials

The clinical stage of development involves the administration of the investigational product to healthy volunteers or patients under the supervision of qualified investigators, generally physicians not employed by or under the trial sponsor's control. Clinical trials must be conducted: (i) in compliance with federal regulations; (ii) in compliance with GCP requirements, and other international standards meant to protect the rights and health of patients and to define the roles of clinical trial sponsors, administrators and monitors; as well as (iii) under protocols detailing, among other things, the objectives of the trial, dosing procedures, subject selection and exclusion criteria, and the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated in the trial, including stopping rules that assure a clinical trial will be stopped if certain AEs should occur. Each protocol involving testing on U.S. patients and subsequent protocol amendments must be submitted to the FDA as part of the IND. Furthermore, each clinical trial must be reviewed and approved by an IRB representing each institution at which the clinical trial will be conducted before the clinical trial commences to ensure that the risks to individuals participating in the clinical trials are minimized and are reasonable in relation to the anticipated benefits. The IRB must conduct continuing review and reapprove the trial at least annually. The IRB also must review and approve, among other things, the trial protocol and informed consent information that must be provided to each clinical trial subject or his or her legal representative and must monitor the clinical trial until completed. Additionally, some clinical trials are overseen by an independent group of qualified experts organized by the clinical trial sponsor, known as a data safety monitoring board or committee. This group provides authorization for whether a trial may move forward at designated checkpoints based on access to certain data from the trial.

A sponsor who wishes to conduct a clinical trial solely outside of the United States may, but need not, obtain FDA authorization to conduct the clinical trial under an IND. Even if a foreign clinical trial is not conducted under an IND, the sponsor may submit data from the clinical trial to the FDA in support of a BLA. The FDA will accept a well- designed and well conducted foreign clinical trial not conducted under an IND if the clinical trial was conducted in accordance with GCP requirements, and the FDA is able to validate the data through an onsite inspection if deemed necessary.

Clinical trials are generally conducted in three sequential phases, known as Phase 1, Phase 2 and Phase 3:

- Phase 1 clinical trials generally involve a small number of healthy volunteers or disease-affected patients who are initially exposed to a single dose and then multiple doses of the product candidate. The primary purpose of these clinical trials is to assess the dosing tolerance, pharmacokinetics, pharmacologic action, side effect tolerability, safety of the product candidate, and, if possible, early evidence of effectiveness.

- Phase 2 clinical trials generally involve studies in disease-affected patients to evaluate proof of concept and/or determine the dosing regimen(s) for subsequent investigations. At the same time, safety and further pharmacokinetic and pharmacodynamic information is collected, possible adverse effects and safety risks are identified, and a preliminary evaluation of efficacy is conducted. Multiple Phase 2 clinical trials may be conducted to obtain information prior to beginning larger and more expensive Phase 3 clinical trials.
- Phase 3 clinical trials generally involve a large number of patients at multiple geographically dispersed trial sites and are designed to provide the data necessary to demonstrate the effectiveness of the product for its intended use, its safety in use and to establish the overall benefit/risk relationship of the product and provide an adequate basis for product labeling. In most cases, the FDA requires two adequate and well-controlled Phase 3 clinical trials to demonstrate the efficacy of the biologic.

These Phases may overlap or be combined. For example, a Phase 1 or 2 clinical trial may contain both a dose-escalation stage and a dose expansion stage, the latter of which may confirm tolerability at the recommended dose for expansion in future clinical trials, as in traditional Phase 1 clinical trials, and provide insight into the anti-tumor effects of the investigational therapy in selected subpopulation(s).

Typically, during the development of oncology therapies, all patients enrolled in Phase 1 clinical trials are disease-affected patients and, as a result, considerably more information on clinical activity may be collected during such trials than during Phase 1 clinical trials for non-oncology therapies. A single Phase 2 or Phase 3 trial with other confirmatory evidence may be sufficient in rare instances to provide substantial evidence of effectiveness, generally subject to the requirement of additional post-approval studies.

In some cases, the FDA may require, or sponsors may voluntarily pursue, post-approval clinical trials, sometimes referred to as Phase 4 clinical trials, after initial marketing approval. These clinical trials are used to gain additional experience from the treatment of patients in the intended therapeutic indication, particularly for long-term safety follow-up.

Phase 1, Phase 2, Phase 3 and other types of clinical trials may not be completed successfully within any specified period, if at all. The FDA, the IRB, or the sponsor may suspend or terminate a clinical trial at any time on various grounds, including non-compliance with regulatory requirements or a finding that patients are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution if the clinical trial is not being conducted in accordance with the IRB's requirements or if the biological product candidate has been associated with unexpected serious harm to patients. Additionally, the data safety monitoring board or committee may recommend halting the clinical trial if it determines that there is an unacceptable safety risk for subjects or other grounds, such as no demonstration of efficacy.

During all phases of clinical development, regulatory agencies require extensive monitoring and auditing of all clinical activities, clinical data, and clinical trial investigators. Annual progress reports detailing the results of the clinical trials must be submitted to the FDA. Written IND safety reports must be promptly submitted to the FDA and the investigators for serious and unexpected AEs, any findings from other studies, tests in laboratory animals or *in vitro* testing that suggest a significant risk for human subjects, or any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure. The sponsor must submit an IND safety report within 15 calendar days after the sponsor determines that the information qualifies for reporting. The sponsor also must notify the FDA of any unexpected fatal or life-threatening suspected adverse reaction within seven calendar days after the sponsor's initial receipt of the information. There also are requirements governing the reporting of ongoing clinical trials and completed clinical trial results to public registries. Information about certain clinical trials, including clinical trial results, must be submitted within specific time frames for publication on the www.clinicaltrials.gov website. Information related to the product, patient population, phase of investigation, clinical trial sites and investigators and other aspects of the clinical trial is then made public as part of the registration. Disclosure of the results of these clinical trials can be delayed in certain circumstances for up to two years after the date of completion of the trial.

Concurrent with clinical trials, sponsors usually complete additional animal studies and also must develop additional information about the chemistry and physical characteristics of the biological product as well as finalize a process for manufacturing the product in commercial quantities in accordance with cGMP requirements. The manufacturing process must be capable of consistently producing quality batches of the product candidate and, among other things, companies must develop methods for testing the identity, strength, quality, potency and purity of the final biological product. Additionally, appropriate packaging must be selected and tested, and stability studies must be conducted to demonstrate that the biologic does not undergo unacceptable deterioration over its shelf life.

FDA Review Process

Following successful completion of all required testing in accordance with all applicable regulatory requirements, the results of product development, preclinical studies and clinical trials are submitted to the FDA as part of a BLA, along with proposed labeling, chemistry and manufacturing information to ensure product quality and other relevant data. To support marketing approval, the data submitted must be sufficient in quality and quantity to establish the safety and efficacy of the investigational product to the satisfaction of the FDA. FDA approval of a BLA must be obtained before a biologic may be marketed in the United States. The cost of preparing and submitting a BLA is substantial. Under the Prescription Drug User Fee Act, or the PDUFA, each BLA must be accompanied by a substantial user fee. The FDA adjusts the PDUFA user fees on an annual basis. Fee waivers or reductions are available in certain circumstances, including a waiver of the application fee for the first application filed by a small business. Additionally, no user fees are assessed on BLAs for products designated as Orphan Drugs, unless the product also includes a non-orphan indication. The applicant under an approved BLA is also subject to an annual program fee.

The FDA reviews all submitted BLAs for completeness before it accepts them for filing and may request additional information. The FDA must make a decision on accepting a BLA for filing within 60 days of receipt, and such decision could include a refusal to file by the FDA for any BLA that it deems incomplete or not properly reviewable at the time of submission. In this event, the BLA must be resubmitted with additional information and the resubmitted application is subject to review to determine if it is substantially complete before the FDA accepts it for filing. Once the submission is accepted for filing, the FDA begins an in-depth review of the BLA. Under the goals and policies agreed to by the FDA under PDUFA, the FDA targets ten months from the filing date in which to complete its initial review of an original BLA and respond to the applicant, and six months from the filing date of an original BLA designated for priority review. The review process for both standard and priority review may be extended by the FDA for three additional months to consider certain late-submitted information, or information intended to clarify information already provided in the submission. The FDA does not always meet its PDUFA goal dates for standard and priority BLAs, and the review process can be significantly extended by FDA requests for additional information or clarification.

Once the submission is accepted for filing, the FDA begins an in-depth substantive review of the BLA. The FDA reviews the BLA to determine, among other things, whether the proposed product is safe, pure and potent for its intended use, and whether the product is being manufactured in accordance with cGMP requirements to ensure its continued safety, purity and potency. The FDA may refer applications for novel products or products that present difficult questions of safety or efficacy to an advisory committee, typically a panel that includes clinicians and other experts, for review, evaluation and a recommendation as to whether the application should be approved and under what conditions, if any. The FDA is not bound by recommendations of an advisory committee, but it generally follows such recommendations when making decisions on approval. The FDA likely will reanalyze the clinical trial data, which could result in extensive discussions between the FDA and the applicant during the review process. During the biological product approval process, the FDA also will determine whether a REMS is necessary to assure the safe use of the biological product. If the FDA concludes a REMS is needed, the sponsor of the BLA must submit a proposed REMS plan; the FDA will not approve the BLA without a REMS, if required.

Before approving a BLA, the FDA will typically conduct a pre-approval inspection of the manufacturing facilities at which the product is manufactured to determine whether they comply with cGMP requirements. The FDA will not approve the product unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. The FDA also may audit clinical trial sites to ensure compliance with GCP requirements and the integrity of the data supporting safety and efficacy. To assure compliance with cGMP and GCP requirements, an applicant must incur significant expenditure of time, money and effort in the areas of training, record keeping, production and quality control.

After the FDA evaluates a BLA and conducts inspections of manufacturing facilities where the investigational product and/or its drug substance will be produced, it will issue either an approval letter or a Complete Response Letter. An approval letter authorizes commercial marketing of the biologic with specific prescribing information for specific indications. A Complete Response Letter indicates that the review cycle of the application is complete and the application will not be approved in its present form. A Complete Response Letter generally outlines the deficiencies that the FDA has identified in the BLA and may require additional clinical data, additional pivotal clinical trial(s) and/or other significant and time-consuming requirements related to clinical trials, preclinical studies or manufacturing in order for the FDA to reconsider the application. Where the FDA determines that the data supporting the application are inadequate to support approval, the FDA may issue a Complete Response Letter without first conducting required inspections, testing submitted product lots, and/or reviewing proposed labeling. In issuing the Complete Response Letter, the FDA may recommend actions that the applicant might take to place the BLA in condition for approval, including requests for additional information or clarification. If a Complete Response Letter is issued, the applicant may either resubmit the BLA, addressing all of the deficiencies identified in the letter, withdraw the application or request an opportunity for a hearing. The FDA has committed to reviewing such resubmissions in two or six months, depending on the type of information included. Even if such data and information are submitted, the FDA may decide that the BLA does not satisfy the criteria for approval, require additional testing or information and/or require post-marketing testing and surveillance to monitor safety or efficacy of a product.

If a product receives regulatory approval, the approval may be significantly limited to specific diseases and dosages or the indications for use may otherwise be limited, including to subpopulations of patients, which could restrict the commercial value of the product. Further, the FDA may require that certain contraindications, warnings, precautions or interactions be included in the product labeling. As a condition of BLA approval, the FDA also may require a REMS to help ensure that the benefits of the biologic outweigh the potential risks to patients. A REMS can include medication guides, communication plans for healthcare professionals and elements to assure a product's safe use, or ETASU. An ETASU can include, but is not limited to, special training or certification for prescribing or dispensing the product, dispensing the product only under certain circumstances, special monitoring and the use of patient-specific registries. The requirement for a REMS can materially affect the potential market and profitability of the product. Moreover, the FDA may require substantial post-approval testing and surveillance to monitor the product's safety or efficacy.

Orphan Drug Designation

Under the Orphan Drug Act, the FDA may grant orphan designation to a drug or biological product intended to treat a rare disease or condition, which is generally a disease or condition that affects fewer than 200,000 individuals in the United States, or 200,000 or more individuals in the United States and for which there is no reasonable expectation that the cost of developing and making the product for this type of disease or condition will be recovered from sales of the product in the United States.

Orphan Drug designation must be requested before submitting a BLA. After the FDA grants Orphan Drug designation, the identity of the therapeutic agent and its potential orphan use are disclosed publicly by the FDA. Orphan Drug designation on its own does not convey any advantage in or shorten the duration of the regulatory review and approval process.

If a product that has orphan designation subsequently receives the first FDA approval for a particular active ingredient for the disease or condition for which it has such designation, the product is entitled to Orphan Drug exclusivity, which means that the FDA may not approve any other applications, including a full BLA, to market the same product for the same indication for seven years from the date of such approval, except in limited circumstances, such as a showing of clinical superiority to the product with orphan exclusivity by means of greater effectiveness, greater safety, or providing a major contribution to patient care, or in instances of drug supply issues. Orphan Drug exclusivity does not prevent the FDA from approving a different product for the same indication or the same product for a different indication. In the latter case, because healthcare professionals are free to prescribe products for off-label uses, the competitor's product could be used for the orphan indication despite another product's orphan exclusivity.

A designated Orphan Drug may not receive Orphan Drug exclusivity if approved for a use that is broader than the indication for which it received orphan designation. In addition, Orphan Drug exclusive marketing rights in the United States may be lost if the FDA later determines that the request for designation was materially defective or, as noted above, if the second applicant demonstrates that its product is clinically superior to the approved product with orphan exclusivity or the manufacturer of the approved product is unable to assure sufficient quantities of the product to meet the needs of patients with the rare disease or condition. Orphan Drug designation may also entitle a party to financial incentives such as opportunities for grant funding towards clinical trial costs, tax advantages and user-fee waivers.

The FDA's determination of whether two ADCs are the same product for purposes of Orphan Drug exclusivity is based on a determination of sameness of the monoclonal antibody element and the functional element of the conjugated molecule. Two ADCs are deemed to be the same product if the complementarity determining region sequences of the antibody and the functional element of the conjugated molecule are the same. A difference in either of those two elements can result in a determination that the molecules are different.

Expedited Development and Review Programs

The FDA is authorized to designate certain product candidates for expedited review if they are intended to address an unmet medical need in the treatment of a serious or life-threatening disease or condition.

Fast Track designation may be granted for product candidates that are intended to treat a serious or life-threatening disease or condition and preclinical or clinical data demonstrate the potential to address unmet medical needs for the condition. Fast Track designation applies to both the product candidate and the specific indication for which it is being studied. The sponsor of a new biological product candidate can request the FDA to designate the candidate for a specific indication for Fast Track status concurrent with, or after, the submission of the IND for the candidate. The FDA must determine if the biological product candidate qualifies for Fast Track designation within 60 days of receipt of the sponsor's request. For Fast Track products, sponsors may have greater interactions with the FDA and the FDA may initiate review of sections of a Fast Track product's BLA before the application is complete. This "rolling review" is available if the FDA determines, after preliminary evaluation of preclinical or clinical data submitted by the sponsor, that a Fast Track product may be effective. The sponsor must also provide, and the FDA must approve, a schedule for the submission of the remaining information for the BLA and the sponsor must pay applicable user fees. Any product candidate submitted to the FDA for marketing, including under a Fast Track program, may be eligible for other types of FDA programs intended to expedite development and review, such as priority review and accelerated approval.

Breakthrough Therapy designation may be granted for product candidates that are intended, alone or in combination with one or more other products, to treat a serious or life-threatening condition and preliminary clinical evidence indicates that the product candidate may demonstrate substantial improvement over available therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. Under the Breakthrough Therapy program, the sponsor of a new biological product candidate may request that the FDA designate the candidate for a specific indication as a Breakthrough Therapy concurrent with, or after, the submission of the IND for the biological product candidate. The FDA must determine if the biological product candidate qualifies for Breakthrough Therapy designation within 60 days of receipt of the sponsor's request. Breakthrough Therapy designation comes with all of the benefits of Fast Track designation. The FDA may take other actions appropriate to expedite the development and review of breakthrough therapies, including holding

meetings with the sponsor throughout the development process, providing timely advice to, and interactive communication with, the sponsor regarding development and approval, involving more senior staff in the review process, assigning a cross-disciplinary project lead for the review team and taking other steps to design the clinical studies in an efficient manner.

Priority review may be granted for product candidates that are intended to treat a serious or life-threatening condition and, if approved, would provide a significant improvement in safety and effectiveness of the treatment, prevention, or diagnosis of a serious condition. The FDA will attempt to direct additional resources to the evaluation of an application designated for priority review in an effort to facilitate the review. Under priority review, the FDA's goal is to review an application in six months once it is filed, compared to ten months for a standard review application.

Accelerated approval may be granted for product candidates that are intended to treat a serious or life-threatening condition and that generally provide a meaningful therapeutic advantage to patients over available treatments and demonstrates an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, or IMM, that is reasonably likely to predict an effect on IMM or other clinical benefit, taking into account the severity, rarity or prevalence of the condition and the availability or lack of alternative treatments. In clinical trials, a surrogate endpoint is a measurement of laboratory or clinical signs of a disease or condition that substitutes for a direct measurement of how a patient feels, functions or survives. The accelerated approval pathway is most often used in settings in which the course of a disease is long, and an extended period of time is required to measure the intended clinical benefit of a product candidate, even if the effect on the surrogate or intermediate clinical endpoint occurs rapidly. Thus, accelerated approval has been used extensively in the development and approval of products for treatment of a variety of cancers in which the goal of therapy is generally to improve survival or decrease morbidity and the duration of the typical disease course requires lengthy and sometimes large trials to demonstrate a clinical or survival benefit. The accelerated approval pathway is contingent on a sponsor's agreement to conduct additional post-approval confirmatory trials to verify and describe the product candidate's clinical benefit. These confirmatory trials must be completed with due diligence and, in some cases, the FDA may require that the trial be designed, initiated and/or fully enrolled prior to approval. Failure to conduct required post-approval studies, or to confirm a clinical benefit during post-marketing studies, would allow the FDA to withdraw the product from the market on an expedited basis. All promotional materials for product candidates approved under accelerated regulations are subject to prior review by the FDA.

Even if a product qualifies for one or more of these programs, the FDA may later decide that the product no longer meets the conditions for qualification or the time period for FDA review or approval may not be shortened. Furthermore, Fast Track designation, Breakthrough Therapy designation, priority review and accelerated approval do not change the standards for approval, but may expedite the development or approval process.

Additional Controls for Biologics

To help reduce the increased risk of the introduction of adventitious agents, the PHSA emphasizes the importance of manufacturing controls for biological product candidates whose attributes cannot be precisely defined. The PHSA also provides authority to the FDA to immediately suspend approvals in situations where there exists a danger to public health, to prepare or procure products in the event of shortages and critical public health needs, and to authorize the creation and enforcement of regulations to prevent the introduction or spread of communicable diseases in the United States and between states.

After a BLA is approved, the product may also be subject to official lot release as a condition of approval. As part of the manufacturing process, the manufacturer is required to perform certain tests on each lot of the product before it is released for distribution. If the product is subject to official release by the FDA, the manufacturer must submit samples of each lot of product to the FDA together with a release protocol showing a summary of the history of manufacture of the lot and the results of all of the manufacturer's tests performed on the lot. The FDA may also perform certain confirmatory tests on lots of some products, such as viral vaccines, before releasing the lots for distribution by the manufacturer.

In addition, the FDA conducts laboratory research related to the regulatory standards on the safety, purity, potency and effectiveness of biological products. As with drugs, after approval of biologics, manufacturers must address any safety issues that arise, are subject to recalls or a halt in manufacturing, and are subject to periodic inspection after approval.

Pediatric Information

Under the Pediatric Research Equity Act, or the PREA, BLAs or supplements to BLAs must contain data to assess the safety and effectiveness of the biological product for the claimed indications in all relevant pediatric subpopulations and to support dosing and administration for each pediatric subpopulation for which the biological product is safe and effective. The FDA may grant full or partial waivers, or deferrals, for submission of data. Unless otherwise required by regulation, PREA generally does not apply to any biological product for an indication for which orphan designation has been granted except that PREA will apply to an original BLA for a new active ingredient that is an orphan-designated biological product if the biological product is a molecularly targeted cancer product intended for the treatment of an adult cancer and is directed at a molecular target that the FDA has determined is substantially relevant to the growth or progression of a pediatric cancer.

The Best Pharmaceuticals for Children Act, or the BPCA, provides a six-month extension of any exclusivity—patent or non-patent—for a biological product if certain conditions are met. Conditions for exclusivity include the FDA’s determination that information relating to the use of a new biologic in the pediatric population may produce health benefits in that population, FDA making a written request for pediatric studies, and the applicant agreeing to perform, and reporting on, the requested studies within the statutory time frame.

Post-Approval Requirements

Once a BLA is approved, a biological product will continue to be subject to rigorous and extensive FDA regulation, particularly with respect to cGMP requirements, product sampling and distribution, reporting of adverse experiences, periodic reporting, and advertising and promotion of the biological product, including standards and regulations for direct-to-consumer advertising, off-label promotion, industry-sponsored scientific and educational activities and promotional activities involving the Internet. Biological products may be marketed only for the approved indications and in a manner consistent with the provisions of the approved labeling.

AE reporting and submission of periodic safety summary reports is required following FDA approval of a BLA. The FDA also may require post-marketing testing, known as Phase 4 testing, REMS, and surveillance to monitor the effects of an approved product, or the FDA may place conditions on an approval that could restrict the distribution or use of the product.

In addition, quality control, biological product manufacture, packaging and labeling procedures must continue to conform to cGMP requirements after approval. Manufacturers of biological products are required to comply with cGMP requirements, including quality control, quality assurance and maintenance of records and documentation. Other post-approval requirements applicable to biological products include reporting of cGMP deviations that may affect the identity, potency, purity and overall safety of a distributed product, record-keeping requirements, reporting of adverse effects, reporting and updated safety and efficacy information, and complying with electronic record and signature requirements.

Biological product sponsors and manufacturers, and certain of their subcontractors, are required to register their establishments with the FDA and certain state agencies. Registration with the FDA subjects entities to periodic unannounced inspections by the FDA, during which the agency inspects a biological product’s manufacturing facilities to assess compliance with cGMP requirements. Accordingly, manufacturers must continue to expend time, money and effort in the areas of production and quality-control to maintain compliance with cGMP requirements. Regulatory authorities may withdraw product approvals or request product recalls if a company fails to comply with required regulatory standards, if it encounters problems following initial marketing, or if previously unrecognized problems are subsequently discovered. In addition, changes to the manufacturing process or facility generally require prior FDA approval before being implemented and other types of the changes to the approved product, such as adding new indications and additional labeling claims, are also subject to further review and approval by the FDA.

Once an approval is granted, the FDA may withdraw the approval if compliance with regulatory requirements and standards is not maintained or if problems occur after the product reaches the market. Later discovery of previously unknown problems with a product, including AEs of unanticipated severity or frequency, or with manufacturing processes or failure to comply with regulatory requirements, may result in revisions to the approved labeling to add new safety information, imposition of post-market studies or clinical trials to assess new safety risks or imposition of distribution or other restrictions under a REMS program. Other potential consequences include, among other things:

- restrictions on the marketing or manufacturing of the product, suspension of the approval, complete withdrawal of the product from the market or product recalls;
- safety alerts, Dear Healthcare Provider letters, press releases or other communications containing warnings or other safety information about the product;
- mandated modification of promotional materials and labeling and issuance of corrective information;
- fines, warning or other enforcement-related letters or holds on clinical trials;
- refusal of the FDA to approve pending BLAs or supplements to approved BLAs, or suspension or revocation of product approvals;
- product seizure or detention, or refusal to permit the import or export of products;
- injunctions or the imposition of civil or criminal penalties; or
- consent decrees, corporate integrity agreements, debarment or exclusion from federal healthcare programs.

Patent Term Restoration and Marketing Exclusivity

Depending upon the timing, duration and specifics of the FDA approval of our product candidates, some of our U.S. patents may be eligible for limited patent term extension under the Drug Price Competition and Patent Term Restoration Act, informally known as the Hatch-Waxman Amendments. The Hatch Waxman Amendments permit a patent term extension of up to five years as compensation for patent term lost during the product development and the FDA regulatory review process. Patent term extension, or PTE, however, cannot extend the remaining term of a patent beyond a total of 14 years from the product's approval date. The PTE period is generally one-half the time between the effective date of an IND and the submission date of a BLA, plus the time between the submission date of a BLA and the approval of that application, except that the review period is reduced by any time during which the applicant failed to exercise due diligence. Only one patent applicable to an approved biological product is eligible for such an extension, only those claims covering the approved drug, a method for using it, or a method for manufacturing it may be extended and the application for the extension must be submitted prior to the expiration of the patent. The USPTO, in consultation with the FDA, reviews and approves the application for any PTE or restoration. Similar provisions are available in Europe and other foreign jurisdictions to extend the term of a patent that covers an approved drug.

Biosimilars and Exclusivity

The Biologics Price Competition and Innovation Act of 2009, or the BPCIA, created an abbreviated approval pathway for biological products shown to be biosimilar to, or interchangeable with, an FDA-licensed reference biological product. Biosimilarity, which requires that the biological product be highly similar to the reference product notwithstanding minor differences in clinically inactive components and that there be no clinically meaningful differences between the biological product and the reference product in terms of safety, purity and potency, can be shown through analytical studies, animal studies and a clinical trial or trials. Interchangeability requires that a biological product be biosimilar to the reference product and that the product must demonstrate that it can be expected to produce the same clinical results as the reference product in any given patient and, for products administered multiple times to an individual, that the product and the reference product may be alternated or switched after one has been previously administered without increasing safety risks or risks of diminished efficacy relative to exclusive use of the reference biological product without such alternation or switch.

A reference biological product is granted 12 years of data exclusivity from the time of first licensure of the product and the FDA will not accept an application for a biosimilar or interchangeable product based on the reference biological product until four years after the date of first licensure of the reference product. “First licensure” typically means the initial date the particular product at issue was licensed in the United States. Date of first licensure does not include the date of licensure of (and a new period of exclusivity is not available for) a biological product if the licensure is for a supplement for the biological product or for a subsequent application by the same sponsor or manufacturer of the biological product (or licensor, predecessor in interest or other related entity) for a change (not including a modification to the structure of the biological product) that results in a new indication, route of administration, dosing schedule, dosage form, delivery system, delivery device or strength, or for a modification to the structure of the biological product that does not result in a change in safety, purity or potency.

The BPCIA is complex and continues to be interpreted and implemented by the FDA. Recent government proposals have sought to reduce the twelve-year reference product exclusivity period. Other aspects of the BPCIA, some of which may impact the BPCIA exclusivity provisions, have also been the subject of recent litigation. As a result, the ultimate impact, implementation and meaning of the BPCIA is subject to significant uncertainty.

International Regulation

In addition to regulations in the United States, a variety of foreign regulations govern clinical trials, commercial sales and distribution of product candidates. The approval process varies from country to country and the time to approval may be longer or shorter than that required for FDA approval.

Other Healthcare Laws and Regulations and Legislative Reform

Healthcare and Privacy Laws and Regulations

Healthcare providers, including physicians, and third-party payors will play a primary role in the recommendation and prescription of any product candidates for which we obtain marketing approval. Our operations, including any arrangements with physicians, other healthcare providers, third-party payors and customers may expose us to broadly applicable fraud and abuse and other healthcare laws that may affect the business or financial arrangements and relationships through which we research as well as market, sell and distribute our products for which we obtain marketing approval. Our current and future operations are subject to regulation by various federal, state and local authorities in addition to the FDA, including but not limited to the Centers for Medicare & Medicaid Services, or CMS, the Department of Health and Human Services, or HHS, including the Office of Inspector General, Office for Civil Rights and the Health Resources and Service Administration, the U.S. Department of Justice, or DOJ, and individual U.S. Attorney offices within the DOJ, and state and local governments. The healthcare laws that may affect our ability to operate include, but are not limited to:

- The federal Anti-Kickback Statute, which prohibits any person or entity from, among other things, knowingly and willfully soliciting, receiving, offering or paying any remuneration, directly or indirectly, overtly or covertly, in cash or in kind, to induce or reward either the referral of an individual for, or the purchase, order or recommendation of an item or service reimbursable, in whole or in part, under a federal healthcare program, such as the Medicare and Medicaid programs. The term “remuneration” has been broadly interpreted to include anything of value. A person or entity does not need to have actual knowledge of the federal Anti-Kickback Statute or specific intent to violate it to have committed a violation. The federal Anti-Kickback Statute has also been interpreted to apply to arrangements between pharmaceutical manufacturers on the one hand and prescribers, purchasers and formulary managers on the other hand. The government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the federal civil False Claims Act, or FCA, or federal civil money penalties statute. There are a number of statutory exceptions and regulatory safe harbors protecting some common activities from prosecution, but the exceptions and safe harbors are drawn narrowly and require strict compliance in order to offer protection.

- Federal civil and criminal false claims laws, such as the FCA, which can be enforced by private citizens through civil qui tam actions, and civil monetary penalty laws prohibit individuals or entities from, among other things, knowingly presenting, or causing to be presented, false, fictitious or fraudulent claims for payment of federal funds, and knowingly making, using or causing to be made or used a false record or statement material to a false or fraudulent claim to avoid, decrease or conceal an obligation to pay money to the federal government. Manufacturers can be held liable under the False Claims Act even when they do not submit claims directly to government payors if they are deemed to “cause” the submission of false or fraudulent claims. In addition, a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the FCA. In addition, manufacturers can be held liable under the FCA even when they do not submit claims directly to government payors if they are deemed to “cause” the submission of false or fraudulent claims.
- The Health Insurance Portability and Accountability Act of 1996, or HIPAA, among other things, imposes criminal liability for knowingly and willfully executing or attempting to execute a scheme to defraud any healthcare benefit program, including private third-party payors, or knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false statement, in connection with the delivery of, or payment for, healthcare benefits, items or services. Similar to the federal Anti-Kickback Statute, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation.
- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009, or HITECH, and their respective implementing regulations, impose requirements on certain covered healthcare providers, health plans, and healthcare clearinghouses as well as their respective business associates that perform services for them that involve the use, or disclosure of, individually identifiable health information as well as their covered subcontractors, relating to the privacy, security, and transmission of such individually identifiable health information.
- Federal and state consumer protection and unfair competition laws, which broadly regulate marketplace activities and activities that potentially harm consumers.
- The federal transparency requirements under the Physician Payments Sunshine Act, created under the Patient Protection and Affordable Care Act, or the Affordable Care Act or ACA, which requires, among other things, certain manufacturers of drugs, devices, biologics and medical supplies reimbursed under Medicare, Medicaid, or the Children’s Health Insurance Program, with certain exceptions, to report annually to CMS information related to payments and other transfers of value provided to physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors), certain other healthcare professionals (such as nurse practitioners and physicians assistants), and teaching hospitals, as well as ownership and investment interests held by physicians and physician’s immediate family members.
- Federal government price reporting laws, which require us to calculate and report complex pricing metrics in an accurate and timely manner to government programs.
- Federal consumer protection and unfair competition laws, which broadly regulate marketplace activities and activities that potentially harm consumers.
- State and foreign laws that are analogous to each of the above federal laws, such as anti-kickback and false claims laws, that may impose similar or more prohibitive restrictions, and may apply to items or services reimbursed by non-governmental third-party payors, including private insurers, and state laws that require manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures and pricing information.

- State and foreign laws that require pharmaceutical companies to implement compliance programs, comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government, or to track and report gifts, compensation and other remuneration provided to physicians and other healthcare providers; state laws that require the reporting of marketing expenditures or drug pricing, including information pertaining to and justifying price increases; state and local laws that require the registration of pharmaceutical sales representatives; and state laws that prohibit various marketing-related activities, such as the provision of certain kinds of gifts or meals; state laws that require the posting of information relating to clinical trials and their outcomes.

Violation of any of the laws described above or any other governmental laws and regulations that may apply to us, may result in significant penalties, including civil, criminal and administrative penalties, damages, fines, exclusion from U.S. government funded healthcare programs, such as Medicare and Medicaid, or similar programs in other countries or jurisdictions, disgorgement, imprisonment, contractual damages, reputational harm, diminished profits, additional reporting requirements and oversight if we become subject to a corporate integrity agreement or similar agreement to resolve allegations of non-compliance with these laws and the delay, reduction, termination or restructuring of our operations.

Legislative Reform

We operate in a highly regulated industry, and new laws, regulations and judicial decisions, or new interpretations of existing laws, regulations and decisions, related to healthcare availability, the method of delivery and payment for healthcare products and services could negatively affect our business, financial condition and prospects. There is significant interest in promoting healthcare reforms, and it is likely that federal and state legislatures within the United States and the governments of other countries will continue to consider changes to existing healthcare legislation.

For example, the United States and state governments continue to propose and pass legislation designed to reduce the cost of healthcare. In 2010, the U.S. Congress enacted the ACA, which included changes to the coverage and reimbursement of drug products under government healthcare programs such as:

- increased the minimum Medicaid rebates owed by manufacturers under the Medicaid Drug Rebate Program;
- established a branded prescription drug fee that pharmaceutical manufacturers of certain branded prescription drugs must pay to the federal government;
- expanded the list of covered entities eligible to participate in the 340B drug pricing program by adding new entities to the program;
- established a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50%, as increased to 70% pursuant to the Bipartisan Budget Act of 2018, effective as of 2019, point-of-sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for the manufacturer's outpatient drugs to be covered under Medicare Part D;
- extended manufacturers' Medicaid rebate liability to covered drugs dispensed to individuals who are enrolled in Medicaid managed care organizations;
- expanded eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to additional individuals and by adding new mandatory eligibility categories for individuals with income at or below 133% of the federal poverty level, thereby potentially increasing manufacturers' Medicaid rebate liability;
- created a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for certain drugs and biologics, including our product candidates, that are inhaled, infused, instilled, implanted or injected;

- established a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research;
- established a Center for Medicare and Medicaid Innovation at the CMS to test innovative payment and service delivery models to lower Medicare and Medicaid spending, potentially including prescription drug spending; and
- created a licensure framework for follow-on biologic products.

Since its enactment, there have been and there remain judicial and congressional challenges to certain aspects of the ACA. For example, since January 2017, former President Trump signed several Executive Orders designed to delay the implementation of certain provisions of the ACA or otherwise circumvent some of the requirements for health insurance mandated by the ACA. While Congress has not passed comprehensive repeal legislation to date, it has enacted laws that modify certain provisions of the ACA such as the Tax Cuts and Jobs Act of 2017, or TCJA, which decreased the “individual mandate” to \$0. On June 17, 2021, the U.S. Supreme Court dismissed the most recent judicial challenge to the ACA brought by several states without specifically ruling on the constitutionality of the ACA. Further, on August 16, 2022, President Biden signed the Inflation Reduction Act of 2022, or IRA, into law, which among other things, extends enhanced subsidies for individuals purchasing health insurance coverage in ACA marketplaces through plan year 2025. The IRA also eliminates the “donut hole” under the Medicare Part D program beginning in 2025 by significantly lowering the beneficiary maximum out-of-pocket cost and creating a new manufacturer discount program. It is possible that the ACA will be subject to judicial or congressional challenges in the future. It is unclear how such challenges and the healthcare reform measures of the Biden administration, will impact the ACA or our business.

In addition, there have been and continue to be a number of initiatives at the U.S. federal and state levels that seek to reduce healthcare costs. In 2011, the U.S. Congress enacted the Budget Control Act, which included provisions intended to reduce the federal deficit. The Budget Control Act resulted in the imposition of 2% reductions in Medicare payments to providers beginning in 2013 and, due to subsequent legislative amendments to the statute, will remain in effect until 2031, absent additional congressional action. Under current legislation the actual reduction in Medicare payments will vary from 1% in 2022 up to 4% in the final year of this sequester. In addition, in 2012, the U.S. Congress enacted the American Taxpayer Relief Act, which, among other things, further reduced Medicare payments to several types of providers, including hospitals, imaging centers and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. If government spending is further reduced, anticipated budgetary shortfalls may also impact the ability of relevant agencies, such as the FDA, to continue to function at current levels, which may impact the ability of relevant agencies to timely review and approve research and development, manufacturing and marketing activities, which may delay our ability to develop, market and sell any product candidates we may develop. Moreover, any significant spending reductions affecting Medicare, Medicaid or other publicly funded or subsidized health programs that may be implemented, or any significant taxes or fees that may be imposed on us, as part of any broader deficit reduction effort or legislative replacement to the Budget Control Act, could have an adverse impact on our anticipated product revenues.

Furthermore, there has been heightened governmental scrutiny over the manner in which manufacturers set prices for their marketed products, which has resulted in several presidential executive orders, congressional inquiries and proposed legislation designed to, among other things, bring more transparency to product pricing, review the relationship between pricing and manufacturer patient programs and reform government program reimbursement methodologies for drug products. At the federal level, in July 2021, the Biden administration released an executive order, “Promoting Competition in the American Economy,” with multiple provisions aimed at prescription drugs. In response to President Biden’s executive order, on September 9, 2021, HHS released a Comprehensive Plan for Addressing High Drug Prices that outlines principles for drug pricing reform and sets out a variety of potential legislative policies that Congress could pursue to advance these principles. Further, the IRA, among other things (i) directs HHS to negotiate the price of certain high-expenditure, single-source drugs and biologics covered under Medicare and (ii) imposes rebates under Medicare Part B and Medicare Part D to penalize price increases that outpace inflation. These provisions will take effect progressively starting in fiscal year 2023, although they may be subject to legal challenges. Additionally, the Biden administration released an additional executive order on October 14, 2022, directing HHS to report on how the Center for Medicare and Medicaid

Innovation can be further leveraged to test new models for lowering drug costs for Medicare and Medicaid beneficiaries.

Individual states in the United States have also become increasingly active in passing legislation and implementing regulations designed to control pharmaceutical product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing. In addition, regional healthcare authorities and individual hospitals are increasingly using bidding procedures to determine what pharmaceutical products and which suppliers will be included in their prescription drug and other healthcare programs.

We expect that additional state and federal healthcare reform measures will be adopted in the future, particularly as a result of the recent presidential election.

Environmental, Health and Safety Laws and Regulations

We and our third-party contractors are subject to numerous environmental, health and safety laws and regulations, including those governing laboratory procedures and the use, generation, manufacture, distribution, storage, handling, treatment, remediation and disposal of hazardous materials and wastes. Hazardous chemicals, including flammable and biological materials, are involved in certain aspects of our business, and we cannot eliminate the risk of injury or contamination from the use, generation, manufacture, distribution, storage, handling, treatment or disposal of hazardous materials and wastes. In particular, our product candidates use PBDs, which are highly potent cytotoxins that require special handling by our and our contractors' staff. In the event of contamination or injury, or failure to comply with environmental, health and safety laws and regulations, we could be held liable for any resulting damages, fines and penalties associated with such liability could exceed our assets and resources. Environmental, health and safety laws and regulations are becoming increasingly more stringent. We may incur substantial costs in order to comply with current or future environmental, health and safety laws and regulations.

Pharmaceutical Coverage, Pricing and Reimbursement

The availability and extent of coverage and adequate reimbursement by governmental and private third-party payors are essential for most patients to be able to afford expensive medical treatments. In both domestic and foreign markets, sales of our product candidates will depend substantially on the extent to which the costs of our product candidates will be covered by third-party payors, such as government health programs, commercial insurance and managed healthcare organizations. These third-party payors decide which products will be covered and establish reimbursement levels for those products.

Coverage and reimbursement by a third-party payor may depend upon a number of factors, including the third-party payor's determination that use of a product is:

- a covered benefit under its health plan;
- safe, effective and medically necessary;
- appropriate for the specific patient;
- cost-effective; and
- neither experimental nor investigational.

Obtaining coverage approval and reimbursement for a product from a government or other third-party payor is a time-consuming and costly process that could require us to provide supporting scientific, clinical and cost-effectiveness data for the use of our products to the payor. We may not be able to provide data sufficient to gain acceptance with respect to coverage and reimbursement at a satisfactory level. If coverage and adequate reimbursement of our future products, if any, are unavailable or limited in scope or amount, such as may result where alternative or generic treatments are available, we may be unable to achieve or sustain profitability.

Adverse coverage and reimbursement limitations may hinder our ability to recoup our investment in our product candidates, even if such product candidates obtain regulatory approval. For products administered under the supervision of a physician, obtaining coverage and adequate reimbursement may be particularly difficult because of the higher prices often associated with such products. Additionally, separate reimbursement for the product itself or the treatment or procedure in which the product is used may not be available, which may impact physician utilization.

There is significant uncertainty related to the insurance coverage and reimbursement of newly approved products. There is no uniform policy for coverage and reimbursement in the United States and, as a result, coverage and reimbursement can differ significantly from payor to payor. In the United States, private payors often, but not always, follow Medicare coverage and reimbursement policies with respect to newly approved products. It is difficult to predict what third-party payors will decide with respect to coverage and reimbursement for fundamentally novel products such as ours, as there is no body of established practices and precedents for these new products. Further, one payor's determination to provide coverage and adequate reimbursement for a product does not assure that other payors will also provide coverage and adequate reimbursement for that product. We may need to conduct expensive pharmaco-economic studies in order to demonstrate the medical necessity and cost-effectiveness of our product candidates. There can be no assurance that our product candidates will be considered medically necessary or cost-effective. In addition to third-party payors, professional organizations and patient advocacy groups such as the NCCN and the American Society of Clinical Oncology can influence decisions about reimbursement for new medicines by determining standards for care. Therefore, it is possible that any of our product candidates, even if approved, may not be covered by third-party payors or the reimbursement limit may be so restrictive that we cannot commercialize the product candidates profitably.

In international markets, reimbursement and health care payment systems vary significantly by country, and many countries have instituted price ceilings on specific products and therapies. In some countries, particularly the countries of the European Union, the pricing of prescription pharmaceuticals is subject to governmental control. In these countries, pricing negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a product. To obtain coverage and reimbursement or pricing approval in some countries, we may be required to conduct a clinical trial that compares the cost-effectiveness of our product candidate to other available therapies. There can be no assurance that our products will be considered cost-effective by third-party payors, that an adequate level of reimbursement will be available or that the third-party payors' reimbursement policies will not adversely affect our ability to sell our products profitably. If reimbursement of our products is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our business could be harmed, possibly materially.

Furthermore, the containment of healthcare costs has become a priority of foreign and domestic governments as well as private third-party payors. The prices of drugs have been a focus in this effort. Governments and private third-party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular medications, which could affect our ability to sell our product candidates profitably. We also expect to experience pricing pressures due to the trend towards managed healthcare, the increasing influence of health maintenance organizations and additional legislative changes. These and other cost-control initiatives could cause us to decrease the price we might establish for products, which could result in lower-than-anticipated product revenues. In addition, the publication of discounts by third-party payors or authorities may lead to further pressure on the prices or reimbursement levels within the country of publication and other countries. If pricing is set at unsatisfactory levels or if coverage and adequate reimbursement of our products is unavailable or limited in scope or amount, our revenues and the potential profitability of our product candidates in those countries would be negatively affected.

PRC Regulation

In the PRC we, through collaborations with our partners, operate in an increasingly complex legal and regulatory environment. We and our collaboration partners are subject to a variety of PRC laws, rules and regulations affecting many aspects of our business. This section summarizes the principal PRC laws, rules and regulations that we believe are relevant to our business and the operations of our partners.

PRC Drug Regulation

Introduction

China heavily regulates the development, approval, manufacturing and distribution of drugs, including biologics. The specific regulatory requirements applicable depend on whether the drug is made and finished in China, which is referred to as a domestically manufactured drug, or made abroad and imported into China in finished form, which is referred to as an imported drug, as well as the approval or “registration” category of the drug. For both imported and domestically manufactured drugs, China typically requires regulatory approval for a Clinical Trial Application, or CTA, to conduct clinical trials in China and submit China clinical trial data, prior to submitting an application for marketing approval. For a domestically manufactured drug, there is also a requirement to have a drug manufacturing license for a facility in China.

In 2017, the drug regulatory system entered a new and significant period of reform. The General Office of the State Council and the General Office of the Central Committee of the China Communist Party jointly issued the Opinion on Deepening the Reform of the Evaluation and Approval System to Encourage Innovation in Drugs and Medical Devices, or the Innovation Opinion, in October 2017. The expedited programs and other advantages under this and other recent reforms encourage drug manufacturers to seek marketing approval in China first, manufacture domestically, and develop drugs in high priority disease areas, such as oncology.

To implement the regulatory reform introduced by the Innovation Opinion, the National People’s Congress of the PRC, or the NPC, and the NMPA, has been revising the fundamental laws, regulations and rules regulating pharmaceutical products and the industry, which include the framework law known as the PRC Drug Administration Law, or DAL. The DAL was promulgated by the Standing Committee of the NPC on September 20, 1984 and last amended on August 26, 2019 and took effect as of December 1, 2019. The DAL is implemented by a high-level regulation issued by the State Council of the PRC referred to as the DAL Implementing Regulation. The NMPA has its own set of regulations further implementing the DAL; the primary one governing CTAs, marketing approval, and post-approval amendment and renewal is known as the Drug Registration Regulation, or the DRR. The trial version of the DRR was promulgated by the China Food and Drug Administration on October 30, 2002, and the last amended DRR was promulgated by the State Administration for Market Regulation, or SAMR, on January 22, 2020, and became effective from July 1, 2020. Although the NMPA has issued several notices and proposed regulations in 2018 and 2019 to implement the reforms, the implementing regulations for many of the reforms in the Innovation Opinion have not yet been finalized and issued, and therefore, the details regarding the implementation of the regulatory changes remained uncertain in some respects.

Regulatory Authorities and Recent Government Reorganization

In the PRC, the NMPA is the primary regulatory agency for pharmaceutical products and businesses. The agency was formed from the former China Food and Drug Administration, or the CFDA, in 2018 as part of a government reorganization. Pursuant to the Decision of the First Session of the Thirteenth National People’s Congress on the State Council Institutional Reform Proposal made by the NPC on March 17, 2018, NMPA is managed by the SAMR, which are responsible for consumer protection, advertising, anti-corruption, pricing and fair competition matters.

Like the CFDA, the NMPA is still the primary drug regulatory agency and implements the same laws, regulations, rules, and guidelines as the CFDA. It also regulates almost all of the key stages of the life-cycle of pharmaceutical products, including nonclinical studies, clinical trials, marketing approvals, manufacturing, advertising and promotion, distribution, and pharmacovigilance (i.e., post-marketing safety reporting obligations). The NMPA’s Center for Drug Evaluation, or CDE, conducts the technical evaluation of each drug and biologic application to assess safety and efficacy.

The National Health Commission of the PRC, or NHC, formerly known as the National Health and Family Planning Commission, or NHFPC, is China’s primary healthcare regulatory agency. It is responsible for overseeing the operation of medical institutions, some of which also serve as clinical trial sites, and regulating the licensure of hospitals and other medical personnel.

Breakthrough Therapy Designation by the NMPA

In July 2020, the NMPA announced the procedure and guidance document for applying and qualifying for Breakthrough Therapy designation. To qualify, a drug has to be intended to treat a serious or life-threatening condition, and demonstrate substantial improvement over available therapies on one or more clinically significant endpoints. Drugs that are designated as breakthrough therapies will receive priority in meeting scheduling and enhanced guidance from the Center for Drug Evaluation, or CDE, to expedite drug development and may also qualify for priority review and conditional approval.

In May 2021, the CDE granted Breakthrough Therapy designation to ARX788 for the second-line treatment of metastatic HER2-positive breast cancer based upon an application by our partner NovoCodex.

Non-Clinical Research

The NMPA requires preclinical data to support registration applications for imported and domestic drugs. According to the DRR, nonclinical safety studies must comply with the Administrative Measures for Good Laboratories Practice of Non-clinical Laboratory. On August 6, 2003, the CFDA promulgated the Administrative Measures for Good Laboratories Practice of Non-clinical Laboratory, which was revised on July 27, 2017, to improve the quality of non-clinical research, and began to conduct the Good Laboratories Practice. Pursuant to the Circular on Administrative Measures for Certification of GLP for Non-clinical Laboratory issued by the CFDA on April 16, 2007, the CFDA is responsible for the certification of non-clinical research institutions nationwide and local provincial medical products administrative authorities is in charge of the daily supervision of non-clinical research institution. The CFDA, and lately the NMPA, decides whether an institution is qualified for undertaking pharmaceutical non-clinical research by evaluating such institution's organizational administration, its research personnel, its equipment and facilities, and its operation and management of non-clinical pharmaceutical projects. A GLP Certification will be issued by the NMPA if all the relevant requirements are satisfied, which will also be published on the NMPA's website.

Clinical Trials and Regulatory Approval

Upon completion of preclinical studies, a sponsor typically needs to conduct clinical trials in China for registering a new drug. The materials required for this application and the data requirements are determined by the registration category. The NMPA has taken a number of steps to increase efficiency for approving CTAs, and it has also significantly increased monitoring and enforcement of the Administrative Regulations of Quality of Drug Clinical Practice, or the PRC's GCP, to ensure data integrity.

Trial Approval

All clinical trials conducted in China for new drug registration purposes must be approved by and conducted at pharmaceutical clinical trial institutions which shall be under the filing administration. For imported drugs, proof of foreign approval is required prior to the trial, unless the drug has never been approved anywhere in the world. In addition to a standalone China trial to support development, imported drug applicants may establish a site in China that is part of an international multicenter trial, or IMCT, at the outset of the global trial. Domestically manufactured drugs are not subject to foreign approval requirements, and in contrast to prior practice, the NMPA has recently decided to permit those drugs to conduct development via an IMCT as well.

In 2015, the CFDA began to issue an umbrella approval for all phases (typically three) of a new drug clinical trial, instead of issuing approval phase by phase. For certain types of new drug candidates, CTAs may be prioritized over other applications and put in a separate expedited queue for approval.

The NMPA has now adopted a system for clinical trials of new drugs where trials can proceed if after 60 business days, the applicant has not received any objections from the CDE. China is also expanding the number of trial sites by changing from a clinical trial site certification procedure into a notification procedure.

Drug Clinical Trial Registration

Pursuant to the DRR, where a clinical trial of drugs is approved, the sponsor shall, prior to conducting subsequent phases of the clinical trial of drugs, formulate the corresponding scheme on the clinical trial of drugs, carry out after review and approval by the Ethics Committee, and submit the corresponding scheme on clinical trials of drugs and supporting materials on the Center for Drug Evaluation website. On September 6, 2013, the CFDA released the Announcement on Drug Clinical Trial Information Platform, or DCTIP, requiring the registration for all clinical trials approved by the CFDA to be completed and trial information to be published through the DCTIP. The applicant shall complete trial pre-registration within one month after obtaining the clinical trial approval to obtain the trial's unique registration number and shall complete registration of certain follow-up information before the first subject's enrollment in the trial. If approval of the foregoing pre-registration and registration is not obtained within one year after obtaining the clinical trial approval, the applicant shall submit an explanation, and if the procedure is not completed within three years, the clinical trial approval shall automatically be annulled.

Pursuant to the DRR, during the period of clinical trial, the applicant must continuously update the registration information and the trial results after completion of each clinical trial on the DCTIP. Applicants are responsible for the authenticity of the registration information.

Human Genetic Resources Approval

According to the Interim Measures for the Administration of Human Genetic Resources, promulgated by the Ministry of Science and Technology and the MOH jointly on June 10, 1998, an additional approval is required for any foreign companies or foreign affiliates that conduct trials in China. On May 28, 2019, the State Council of the PRC issued the Administration Regulations on Human Genetic Resources, which became effective on July 1, 2019, and superseded the Interim Measures for the Administration of Human Genetic Resources. The Administration Regulations on Human Genetic Resources formalized the approval requirements pertinent to research collaborations between Chinese and foreign-owned entities. Pursuant to the new rule, a new notification system, as opposed to the advance approval approach originally in place, is put in place for clinical trials using China's human genetic resources at clinical institutions without involving the export of human genetic resources outside of China.

On July 2, 2015, the Ministry of Science and Technology issued the Service Guide for Administrative Licensing Items concerning Examination and Approval of Sampling, Collecting, Trading, Exporting Human Genetic Resources, or Taking Such Resources out of the PRC, which provides that foreign-invested sponsors that sample and collect human genetic resources in clinical trials are required to file with the China Human Genetic Resources Management Office through its online system. On October 26, 2017, the Ministry of Science and Technology issued the Circular on Optimizing the Administrative Examination and Approval of Human Genetic Resources, which simplified the approval for sampling and collecting human genetic resources for the purpose of commercializing a drug in the PRC.

On October 17, 2020, the Standing Committee of the NPC promulgated the Biosecurity Law of the PRC, which will become effective from April 15, 2021. The new law restates the approval and notification requirements of human genetic resources sampling, collecting, utilizing and exporting, as provided in the Administration Regulations on Human Genetic Resources. Moreover, the promulgation of the new law, which takes the form of national law, further demonstrates the commitments of protecting China's human genetic resources and safeguarding state biosecurity by the PRC government.

Trial Exemptions and Acceptance of Foreign Data

The NMPA may reduce requirements for clinical trials and data, depending on the drug and the existing data. The NMPA has granted waivers for all or part of trials and has stated that it will accept data generated abroad (even if not part of a global study), including early phase data, that meets its requirements. On July 6, 2018, the NMPA issued the Technical Guidance Principles on Accepting Foreign Drug Clinical Trial Data, or the Guidance Principles, as one of the implementing rules for the Innovation Opinion. According to the Guidance Principles, the data of foreign clinical trials must meet the authenticity, completeness, accuracy and traceability requirements and such data must be obtained consistent with the relevant requirements under the GCP of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use, or ICH. Sponsors must be attentive to potentially meaningful ethnic differences in the subject population.

Clinical Trial Process and Good Clinical Practices

Typically drug clinical trials in China have four phases. Phase 1 refers to the initial clinical pharmacology and human safety evaluation studies. Phase 2 refers to the preliminary evaluation of a drug candidate's therapeutic efficacy and safety for target indication(s) in patients. Phase 3, often the pivotal study, refers to clinical trials to further verify the drug candidate's therapeutic efficacy and safety in patients with target indication(s) and ultimately provide sufficient evidence for the review of a drug registration application. Phase 4 refers to a new drug's post-marketing study to assess therapeutic effectiveness and adverse reactions when the drug is widely used to evaluate overall benefit-risk relationships of the drug when used among the general population or specific groups and to adjust the administration dose, etc. The NMPA requires that the different phases of clinical trials in China receive ethics committee approval and comply with the PRC's GCP. The NMPA conducts inspections to assess the PRC's GCP compliance and will cancel the CTA if it finds substantial issues.

On August 6, 2003, the CFDA promulgated the PRC's GCP, which was amended by NMPA and NHC on April 23, 2020 and took effect on July 1, 2020, to improve the quality of clinical trials. According to the PRC's GCP, the sponsor shall provide insurance to the subjects participating in the clinical trial and bear the cost of the treatment and the corresponding financial compensation for the subjects who suffer harm or death related to the trial. The sponsor shall provide legal and economic guarantee to the investigator, but harm or death caused by the medical accident shall be excluded. Pursuant to the Innovation Opinion, the accreditation of the institutions for drug clinical trials shall be subject to record-filing administration. The conduct of clinical trials must adhere to the PRC's GCP, and the protocols must be approved by the ethics committees of each study site. Pursuant to the newly amended DAL, and the Regulations on the Administration of Drug Clinical Trial Institution jointly promulgated by NMPA and NHC on November 29, 2019 and effective from December 1, 2019, drug clinical trial institutions shall be under filing administration. Entities that only conduct analysis of biological samples related to clinical trials of drugs do not need to be filed.

New Drug Application, or NDA, and Approval

According to the DRR, the applicant may submit an application for drug marketing registration to CDE upon completion of relevant research on pharmacy, pharmacology, toxicology and drug clinical trials, determination the quality standards of the drug, validation of commercial-scale production processes and preparation for acceptance of verification and inspection conducted by professional technical institution designated by competent NMPA. The CDE will organize pharmaceutical, medical and other technicians to conduct comprehensive review of the safety, efficacy and quality controllability, among others, of the drug according to the application materials submitted by the applicant, the results of the verification and inspection conducted by professional technical institution, etc. If the comprehensive review conclusion is affirmative, the drug shall be approved for marketing and a drug registration certificate will be issued containing the information of the drug approval number, the marketing authorization holders and the manufacturer. Pursuant to the Opinions on the Reform of Evaluation and Approval System for Drugs and Medical Devices and Equipment promulgated on August 9, 2015, the State Council published the policy for carrying out a pilot plan for the drug marketing authorization holder mechanism.

Pursuant to the newly amended DAL, under the drug marketing authorization holder mechanism, an enterprise obtained drug registration certificate and a research and development institution are eligible to be a pharmaceutical marketing authorization holder, and this pharmaceutical marketing authorization holder shall be responsible for nonclinical laboratory studies, clinical trials, production and distribution, post-market studies, and the monitoring, reporting, and handling of adverse reactions in connection with pharmaceuticals in accordance with the provisions of the DAL. The pharmaceutical marketing authorization holder may engage contract manufacturers for manufacturing, provided that the contract manufacturers are licensed and may engage pharmaceutical distribution enterprises with drug distribution license for the distribution activities. Upon the approval of the medical products administrative department under the State Council, a drug marketing authorization holder may transfer the drug marketing license and the transferee shall have the capability of quality management, risk prevention and control, and liability compensation to ensure the safety, effectiveness and quality controllability of drugs, and fulfill the obligations of the drug marketing license holder.

Human Cell Therapy

On March 20, 2003, the CFDA published the Technical Guidelines for Research on Human Cell Therapy and Quality Control of Preparations, which set some principles for the research of human cell therapy.

Pursuant to the DRR promulgated by the CFDA on July 10, 2007 and effective from October 1, 2007, human cell therapy and its products belong to biological products and the application for biological products shall be submitted as the process of new drug application.

On March 2, 2009, the MOH published the Management Measures for Clinical Application of Medical Technology, which came into effect on May 1, 2009 and prescribed that cell immunotherapy belongs to the Category 3 medical technology of which the clinical application shall be subject to the additional provisions of the MOH. In May 2009, the MOH published the First List of Category 3 Medical Technologies Allowed for Clinical Application, or the Category 3 Medical Technologies, which prescribed cell immunotherapy technology as Category 3 medical technologies were allowed for clinical application, and was abolished by the Notice on the Relevant Work Concerning Cancellation of the Category Three of Medical Technology Entry Approval of Clinical Application on June 29, 2015. The Notice on the Relevant Work Concerning Cancellation of the Category Three of Medical Technology Entry Approval of Clinical Application also canceled the approval of Category 3 medical technology clinical application.

On November 30, 2017, the CFDA promulgated the Notice of Guidelines for Acceptance and Examination of Drug Registration, the application of clinical trials of therapeutic biological products and the production and listing application of therapeutic biological products shall be subject to the provisions thereof. On December 18, 2017, the CFDA promulgated the Technical Guiding Principles for Research and Evaluation of Cell Therapy Products to regulate and guide the research and evaluation of cell therapy products that are researched on, developed and registered as drugs.

Commercial Bribery

Pharmaceutical companies involved in a criminal investigation or administrative proceedings related to bribery are listed in the Adverse Records of Commercial Briberies by their respective provincial health commissions. Pursuant to the Provisions on the Establishment of Adverse Records of Commercial Briberies in the Medicine Purchase and Sales Industry which were promulgated by the NHFPC on December 25, 2013 and became effective on March 1, 2014, provincial health commissions formulate the implementing measures for establishment of Adverse Records of Commercial Briberies. Where a pharmaceutical company or its agent is listed in the Adverse Records of Commercial Briberies on one occasion, it will be prohibited from participating in the procurement bidding process or selling its products to public medical institutions located in the local provincial-level region for two years from the publication of the adverse records. Where a pharmaceutical company or its agent is listed in the Adverse Records of Commercial Briberies on two or more occasions within five years, it will be prohibited from participating in the procurement bidding process or selling its products to all public medical institutions in the PRC for two years from the publication of these adverse records.

Other PRC National- and Provincial-Level Laws and Regulations

We are subject to changing regulations under many other laws and regulations administered by governmental authorities at the national, provincial and municipal levels, some of which are or may become applicable to our business. For example, regulations control the confidentiality of patients' medical information and the circumstances under which patient medical information may be released for inclusion in our databases or released by us to third parties. The privacy of human subjects in clinical trials is also protected under regulations. For example, the case report forms must avoid disclosing names of the human subjects.

These laws and regulations governing both the disclosure and the use of confidential patient medical information may become more restrictive in the future, including restrictions on transfer of healthcare data. The Cybersecurity Law that took effect in 2017 designates healthcare as a priority area that is part of critical information infrastructure, and China's cyberspace administration is working to finalize a draft rule on cross-border transfer of personal information.

PRC Regulation of Foreign Investment

Investment activities in China by foreign investors are principally governed by the Guidance Catalogue of Industries for Foreign Investment, or the Catalogue, which was promulgated and is amended from time to time by the MOFCOM and the NDRC. Pursuant to the latest Catalogue which came into effect in July 2018 with the latest amendment being effective as of July 2020, or the 2020 Catalogue, industries are divided into two categories: encouraged industries and the industries within the catalogue of special management measures, or the Negative List. The Negative List is further divided into two sub-categories: restricted industries and prohibited industries. Establishment of wholly foreign-owned enterprises is generally allowed in industries outside of the Negative List. For the restricted industries within the Negative List, some are limited to equity or contractual joint ventures, while in some cases Chinese partners are required to hold the majority interests in such joint ventures. Foreign investors are not allowed to invest in industries in the prohibited category. Industries not listed in the Catalogue are generally open to foreign investment unless specifically restricted by other PRC regulations.

On March 15, 2019, the NPC approved the Foreign Investment Law of the PRC, or the Foreign Investment Law, which became effective on January 1, 2020 and replaced the PRC Equity Joint Venture Law, the PRC Cooperation Joint Venture Law and the Wholly Foreign-Owned Enterprise Law, together with their implementation rules and ancillary regulations. According to the Foreign Investment Law, "foreign investment" refers to investment activities directly or indirectly conducted by one or more natural persons, business entities, or other organizations of a foreign country, collectively referred to as "foreign investor", within China. Under the Foreign Investment Law, "investment activities" include: (i) a foreign investor, individually or together with other investors, establishes a foreign-invested enterprise within China; (ii) a foreign investor acquires stock shares, equity shares, shares in assets, or other similar rights and interests of an enterprise within China; (iii) a foreign investor, individually or together with other investors, invests in a new construction project within China; and (iv) other types of investments as provided by the laws, regulations or the State Council of the PRC. The Foreign Investment Law grants national treatment to foreign invested entities, except for those foreign invested entities that operate in industries deemed to be either "restricted" or "prohibited" in the Negative List.

On December 26, 2019, the State Council of the PRC promulgated the Implementation Rules to the Foreign Investment Law, which became effective on January 1, 2020. The implementation rules further clarified that the state encourages and promotes foreign investment, protects the lawful rights and interests of foreign investors, regulates foreign investment administration, continues to optimize foreign investment environment, and advances a higher level opening.

On December 30, 2019, the MOFCOM and the SAMR jointly promulgated Measures for Reporting of Foreign Investment Information, which became effective on January 1, 2020. Under this regulation, since January 1, 2020, for foreign investors carrying out investment activities directly or indirectly in the PRC, foreign investors or foreign-invested enterprises shall submit investment information through the Enterprise Registration System and the National Enterprise Credit Information Publicity System operated by the SAMR.

Regulations Relating to Foreign Exchange

The PRC Foreign Exchange Administration Regulations promulgated by the State Council of the PRC on January 29, 1996, which was amended on January 14, 1997 and August 5, 2008, respectively, are the principal regulations governing foreign currency exchange in China. Under the PRC foreign exchange regulations, payments of current account items, such as profit distributions and trade and service-related foreign exchange transactions, may be made in foreign currencies without prior approval from the State Administration of Foreign Exchange, or SAFE, by complying with certain procedural requirements. In contrast, approval from or registration with appropriate government authorities or designated banks is required when RMB is to be converted into a foreign currency and remitted out of China to pay capital expenses such as the repayment of foreign currency-denominated loans.

Under current regulations, the capital of a foreign-invested enterprise and capital in RMB obtained by the foreign-invested enterprise from foreign exchange settlement may not be used for the following purposes: (i) directly or indirectly used for the payment beyond the business scope of the enterprises or the payment prohibited by relevant laws and regulations; (ii) directly or indirectly used for investment in securities, unless otherwise provided by relevant laws and regulations; (iii) extending loans to non-related parties, unless permitted by the scope of business; or (iv) paying the expenses related to the purchase of real estate that is not for self-use, except for the real estate enterprises.

In 2017, new regulations were adopted which, among other things, relax the policy restriction on foreign exchange inflow to further enhance trade and investment facilitation and tighten genuineness and compliance verification of cross-border transactions and cross-border capital flows.

In 2019, SAFE promulgated SAFE Circular 28, which canceled restrictions on domestic equity investments made with capital funds by non-investing foreign-funded enterprises. If a non-investing foreign-funded enterprise makes domestic equity investment with capital funds obtained from foreign exchange settlement, the investee shall undergo registration formalities for accepting domestic reinvestment and open the “capital account—account for settled foreign exchange to be paid” to receive the corresponding funds according to relevant provisions.

SAFE Circular 37

In July 2014, SAFE promulgated SAFE Circular 37, which replaces the previous SAFE Circular 75. SAFE Circular 37 requires PRC residents, including PRC individuals and PRC corporate entities, to register with SAFE or its local branches in connection with their direct or indirect offshore investment activities. SAFE Circular 37 is applicable to our shareholders who are PRC residents and may be applicable to any offshore acquisitions that we may make in the future.

Under SAFE Circular 37, PRC residents who make, or have prior to the implementation of SAFE Circular 37 made, direct or indirect investments in offshore special purpose vehicles, or SPVs, are required to register such investments with SAFE or its local branches. In addition, any PRC resident who is a direct or indirect shareholder of an SPV, is required to update its registration with the local branch of SAFE with respect to that SPV, to reflect any change of basic information or material events. If any PRC resident shareholder of such SPV fails to make the required registration or to update the registration, the subsidiary of such SPV in China may be prohibited from distributing its profits or the proceeds from any capital reduction, share transfer or liquidation to the SPV, and the SPV may also be prohibited from making additional capital contributions into its subsidiaries in China. In February 2015, SAFE promulgated SAFE Notice 13. Under SAFE Notice 13, applications for foreign exchange registration of inbound foreign direct investments and outbound direct investments, including those required under SAFE Circular 37, must be filed with qualified banks instead of SAFE. Qualified banks should examine the applications and accept registrations under the supervision of SAFE.

On April 10, 2020, SAFE promulgated the Circular on Optimizing Administration of Foreign Exchange to Support the Development of Foreign-related Business, which allows eligible enterprises to make domestic payments using their capital funds, foreign credits and the income under capital accounts of overseas listing, without providing evidentiary materials concerning authenticity of such capital for banks in advance, provided that their capital use shall be authentic and in line with provisions, and conform to the prevailing administrative regulations on the use of income under capital accounts. The administering bank shall perform ex-post sampling in accordance with the relevant requirements.

Regulations Relating to Outbound Direct Investment

On December 26, 2017, the NDRC promulgated the Administrative Measures on Overseas Investments, or NDRC Order No. 11, which took effect as of March 1, 2018. According to NDRC Order No. 11, non-sensitive overseas investment projects are subject to record-filing requirements with the local branch of the NDRC. On September 6, 2014, MOFCOM promulgated the Administrative Measures on Overseas Investments, which took effect as of October 6, 2014. According to this regulation, overseas investments of PRC enterprises that involve non-sensitive countries and regions and non-sensitive industries are subject to record-filing requirements with a local MOFCOM branch. According to the Circular of the State Administration of Foreign Exchange on Issuing the Regulations on Foreign Exchange Administration of the Overseas Direct Investment of Domestic Institutions, which was promulgated by SAFE on July 13, 2009 and took effect on August 1, 2009, PRC enterprises must register for overseas direct investment with a local SAFE branch.

The Circular on Further Simplifying and Improving Foreign Exchange Administration Policies in Respect of Direct Investment, which was promulgated in February 2015 and effective in June 2015 and further amended in December 2019, provides that PRC enterprises may register with qualified banks instead of the SAFE in connection with their establishment or control of an offshore entity established for the purpose of overseas direct investment.

Rest of World Regulation

For other countries outside of the United States and the PRC, the requirements governing the conduct of clinical trials, drug licensing, pricing and reimbursement vary from country to country. In all cases the clinical trials must be conducted in accordance with GCP requirements and the applicable regulatory requirements and the ethical principles having their origin in the Declaration of Helsinki.

Employees and Human Capital

As of December 31, 2022, we had 66 total and full-time employees, 23 of whom hold Ph.D. and/or M.D. degrees. Of these 66 employees, 47 were engaged in research and development activities and 19 were engaged in business development, finance, information systems, facilities, human resources or administrative support. One of the employees was based in Shanghai, China while the other 65 resided in the United States. None of our employees are subject to a collective bargaining agreement. We consider our relationship with our employees to be good.

Our human capital resources objectives include, as applicable, identifying, recruiting, retaining, incentivizing and integrating our existing and new employees, advisors and consultants. The principal purposes of our equity incentive plans are to attract, retain and reward personnel through the granting of share-based compensation awards in order to increase shareholder value and the success of our company by motivating such individuals to perform to the best of their abilities and achieve our objectives.

Corporate Information

Ambrx commenced its operations in the United States in January 2003 when Ambrx Inc., or Ambrx US, was incorporated in Delaware. In May 2015, Ambrx incorporated under the laws of the Cayman Islands and became the ultimate holding company, or Ambrx Cayman, through a series of transactions. The Company owns 100% of Shanghai Ambrx Biopharma Company Limited, or Ambrx Shanghai, and Biolaxy Pharmaceutical Hong Kong Limited, a company incorporated in Hong Kong, or Ambrx HK. Ambrx HK owns 100% of Ambrx US, and Ambrx US owns 100% of Ambrx Australia Pty Limited, a company incorporated in Australia, or Ambrx AU. Ambrx US is based in San Diego, California.

Our principal executive offices are located at 10975 North Torrey Pines Road, La Jolla, California 92037. Our telephone number at this address is (858) 875-2400. Our registered office in the Cayman Islands is located at the offices of Maples Corporate Services Limited, PO Box 309, Ugland House, Grand Cayman, KY1-1104, Grand Cayman KY1-1104, Cayman Islands. Investors should submit any inquiries to the address and telephone number of our principal executive offices set forth above.

“Ambrx,” the Ambrx logo and other trademarks or service marks of Ambrx Biopharma Inc. appearing in this Annual Report are the property of Ambrx Biopharma Inc. Trademarks, trade names, and service marks of other companies appearing in this Annual Report are the property of their respective holders.

Financial and other information about our company is available on our website at www.ambrx.com. We make available on our website, free of charge, copies of our Annual Report on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and amendments to those reports filed or furnished pursuant to Section 13(a) or 15(d) of the Securities Exchange Act of 1934, as amended, or the Exchange Act, as soon as reasonably practicable after we electronically file such material with, or furnish it to, the SEC. We may use our website as a means of disclosing material non-public information and for complying with our disclosure obligations under Regulation Fair Disclosure promulgated by the SEC. These disclosures will be included on our website under the “Investors” section. All reports we file with the SEC are available free of charge via EDGAR through the SEC website at www.sec.gov. We have included the web addresses of Ambrx Biopharma Inc. and the SEC as inactive textual references only. Except as specifically incorporated by reference into this Annual Report, information on these websites is not part of this filing.

Emerging Growth Company and Smaller Reporting Company

We are an “emerging growth company” as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act. We may take advantage of certain exemptions from various public company reporting requirements, including not being required to have our internal control over financial reporting audited by our independent registered public accounting firm under Section 404 of the Sarbanes-Oxley Act of 2002, or the Sarbanes-Oxley Act, reduced disclosure obligations regarding executive compensation in our periodic reports and proxy statements, and exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and any golden parachute payments. We may take advantage of these exemptions until December 31, 2026 or until we are no longer an “emerging growth company,” whichever is earlier. We will cease to be an emerging growth company prior to the end of such period if certain earlier events occur, including if we become a “large accelerated filer” as defined in Rule 12b-2 under the Exchange Act, our annual gross revenues exceed \$1.235 billion or we issue more than \$1.0 billion of non-convertible debt in any three-year period.

In addition, the JOBS Act provides that an emerging growth company can take advantage of an extended transition period for complying with new or revised accounting standards. This provision allows an emerging growth company to delay the adoption of accounting standards that have different effective dates for public and private companies until those standards would otherwise apply to private companies. We have not elected to avail ourselves of this exemption and, therefore, we will be subject to the same new or revised accounting standards as other public companies that are not “emerging growth companies.”

We are also a “smaller reporting company” as defined in the Exchange Act. We may continue to be a smaller reporting company even after we are no longer an emerging growth company. We may take advantage of certain of the scaled disclosures available to smaller reporting companies and will be able to take advantage of these scaled disclosures for so long as our voting and non-voting common stock held by non-affiliates is less than \$250.0 million measured on the last business day of our second fiscal quarter, or our annual revenue is less than \$100.0 million during the most recently completed fiscal year and our voting and non-voting common stock held by non-affiliates is less than \$700.0 million measured on the last business day of our second fiscal quarter.

Item 1A. Risk Factors.

An investment in our American Depositary Shares, or ADSs, involves a high degree of risk. The occurrence of any of the events or developments described below could harm our business, financial condition, results of operations and/or prospects or cause our actual results to differ materially from those contained in forward-looking statements we have made in this Annual Report and those we may make from time to time. In such an event, the market price of our ADSs could decline and you may lose all or part of your investment. You should consider all of the risk factors described when evaluating our business.

Risks Related to Our Financial Position, Capital Requirements and Limited Operating History

We have incurred net losses since our inception and anticipate that we will continue to incur significant losses for the foreseeable future. We may never generate any revenue or become profitable or, if we achieve profitability, may not be able to sustain it.

We have never generated any revenue from product sales and have incurred net losses each year since we commenced operations. For the years ended December 31, 2022 and 2021, our net loss attributable to our shareholders was \$78.0 million and \$68.1 million, respectively. We expect that it will be several years, if ever, before we have a product candidate that will achieve regulatory approval and be commercialized. We expect to incur increasing levels of operating losses over the next several years and for the foreseeable future as we advance our product candidates through clinical development. Our prior losses, combined with expected future losses, have had and will continue to have an adverse effect on our shareholders' equity and working capital.

To become and remain profitable, we must develop and eventually commercialize a product or products with significant market potential. This will require us to be successful in a range of challenging activities, including completing preclinical studies and clinical trials of our product candidates, obtaining marketing approval for these product candidates, manufacturing, marketing and selling those products for which we may obtain marketing approval and satisfying any post-marketing requirements. We may never succeed in these activities and, even if we succeed in commercializing one or more of our product candidates, we may never generate revenue that is significant enough to achieve profitability. If we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis and we will continue to incur substantial research and development and other expenditures to develop and market additional product candidates. Our failure to become and remain profitable could decrease the value of our ADSs and impair our ability to raise capital, maintain our research and development efforts, expand our business or continue our operations.

Our limited operating history may make it difficult for you to evaluate the success of our business to date and to assess our future viability.

We are a clinical-stage biologics company with a limited operating history. As an organization, we have not demonstrated an ability to successfully complete late-stage clinical trials, obtain regulatory approvals, manufacture our product candidates at commercial scale or arrange for a third party to do so on our behalf, conduct sales and marketing activities necessary for successful commercialization, or obtain reimbursement in the countries of sale. We may encounter unforeseen expenses, difficulties, complications, and delays in achieving our business objectives. Our short history as an operating company makes any assessment of our future success or viability subject to significant uncertainty. If we do not address these risks successfully or are unable to transition at some point from a company with a research and development focus to a company capable of supporting commercial activities, then our business will be materially harmed.

We will need to obtain substantial additional funding to complete the development and commercialization of our product candidates. If we are unable to raise this capital when needed, we may be forced to delay, reduce or eliminate our product development programs or other operations.

Since our inception, we have financed our operations primarily through sales of our shares and funding from our collaborations. The development of biological product candidates is capital intensive. As our product candidates enter and advance through preclinical studies and clinical trials, we will need substantial additional funds to pay external development costs and expand our clinical, regulatory, quality and manufacturing capabilities. If we obtain marketing approval for any of our product candidates, we expect to incur significant commercialization expenses related to marketing, sales, manufacturing and distribution. Furthermore, we have incurred and expect to incur additional costs associated with operating as a public company.

As of December 31, 2022, we had cash, cash equivalents and marketable debt securities, available-for-sale, or MDS, of \$101.3 million, of which \$16.8 million are non-current MDS. Based upon our current operating plan, we estimate that our existing cash, cash equivalents and MDS will be sufficient to fund our operating expenses and capital expenditure requirements for at least the next 12 months from the date of this Annual Report.

We have based these estimates on assumptions that may prove to be incorrect or require adjustment as a result of business decisions, and we could utilize our available capital resources sooner than we currently expect. Our future capital requirements will depend on many factors, including:

- the initiation, trial design, progress, timing, costs and results of drug discovery, preclinical studies and clinical trials of our product candidates;
- the number and characteristics of product candidates that we pursue, as well as the indications for which we develop our product candidates;
- the length of our clinical trials, including, among other things, as a result of delays in enrollment, difficulties enrolling sufficient subjects or delays or difficulties in clinical trial site initiations;
- the outcome, timing and costs of seeking regulatory approvals for our product candidates;
- the costs of manufacturing our product candidates, in particular for clinical trials in preparation for marketing approval and in preparation for commercialization;
- the costs of any third-party products used in our combination clinical trials that are not covered by such third party or other sources;
- the costs associated with hiring additional personnel and consultants as our preclinical, manufacturing, regulatory and clinical activities increase;
- whether and when we receive marketing approvals and revenue from any commercial sales of any of our product candidates, if approved;
- the cost of commercialization activities for any of our product candidates, if approved, including marketing, sales and distribution costs;
- the emergence of competing therapies and other adverse market developments;
- the ability to establish and maintain strategic collaboration, licensing or other arrangements and whether and when we receive or are obligated to make payments under such arrangements;
- the extent to which we are able to internally develop or license ARX788 for external development and commercialization outside of China, if pursued;
- the extent to which we in-license or acquire other products and technologies and the terms of these transactions;
- the costs involved in preparing, filing, prosecuting, maintaining, expanding, defending and enforcing patent claims, including litigation costs and the outcome of such litigation;

- our need and ability to retain key management and hire scientific, technical, business, and medical personnel;
- our implementation of additional internal systems and infrastructure, including operational, financial and management information systems;
- the costs associated with expanding our facilities or building out our laboratory space;
- changes to development plans with respect to our product candidates;
- the extent of the impacts and duration of geopolitical and macroeconomic events, including the ongoing COVID-19 pandemic, conflict between Ukraine and Russia and bank failures; and
- the costs of operating as a public company.

Because we do not expect to generate revenue from product sales for several years, if at all, we will need to obtain substantial additional funding in connection with our continuing operations and expected increases in expenses. Until such time as we can generate significant revenue from sales of our product candidates, if ever, we expect to finance our cash needs through equity offerings, debt financings or other capital sources, including potentially grants, collaborations, licenses or other similar arrangements. In addition, we may seek additional capital due to favorable market conditions or strategic considerations, even if we believe we have sufficient funds for our current or future operating plans. The impact of the recent disruption in access to bank deposits and lending commitments due to bank failures, the COVID-19 pandemic, the ongoing conflict between Ukraine and Russia, changes in interest rates and economic inflation on capital markets may affect the availability, amount and type of financing available to us in the future. If we are unable to raise capital when needed or on attractive terms, we would be forced to delay, reduce or eliminate our research and development programs or future commercialization efforts.

Raising additional capital may cause dilution to our shareholders restrict our operations or require us to relinquish rights to our technologies or product candidates.

Until such time, if ever, as we can generate substantial product revenue, we expect to finance our operations through equity offerings, debt financings or other capital sources, including potentially grants, collaborations, licenses or other similar arrangements. To the extent that we raise additional capital through the sale of equity or convertible debt securities, your ownership interest will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect your rights as an ADS holder. Debt financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as limitations on our ability to incur additional debt, make capital expenditures or declare dividends.

If we raise funds through collaborations or licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies, future revenue streams, research programs or product candidates or grant licenses on terms that may not be favorable to us. If we are unable to raise additional funds when needed, we may be required to delay, limit, reduce or terminate our product development or future commercialization efforts or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

Risks Related to the Discovery, Development and Regulatory Approval of Our Product Candidates

We are early in our development efforts and have a limited history of conducting clinical trials to test our product candidates in humans.

We are early in our development efforts and most of our operations to date have been limited to developing our platform technologies and conducting drug discovery and preclinical studies. As a result, there are many steps in the drug development process that we must still successfully complete and have limited experience with as a company.

Our ability to successfully complete development of any of our current and future product candidates will depend on a number of factors, including:

- successful completion of preclinical studies;
- submission of Investigational New Drug, or IND, or other regulatory applications to allow for initiation of our planned and future clinical trials and authorizations from regulators to initiate clinical trials;
- successful initiation, execution and completion of, planned and future clinical trials and achieving positive safety and efficacy results from such trials;
- demonstrating a risk-benefit profile acceptable to regulatory authorities;
- clinical trial data that are sufficient to support marketing approvals from applicable regulatory authorities; and
- obtaining and maintaining patent, trade secret and other intellectual property protection and regulatory exclusivity for our product candidates and avoiding infringement of third-party intellectual property rights.

If we do not achieve one or more of these requirements in a timely manner, we could experience significant delays or an inability to successfully complete development of our product candidates, which would materially harm our business.

We recently engaged in a strategic reprioritization of our product pipeline. Such strategic reprioritization may cause us to expend our limited resources to pursue a particular product candidate and fail to capitalize on product candidates or indications that may be more profitable or for which there is a greater likelihood of success and could harm our future business prospects.

On October 18, 2022, we announced a reprioritization of our product pipeline after conducting a strategic assessment that considered our cash runway and our product pipeline near term value creation opportunities, among other factors. As a result of our assessment, we paused the internal development of ARX788 and, among other potential activities, planned to seek development partners to further its development outside of China. In the first quarter of 2023, we decided to conduct a signal-finding study in the post-Enhertu metastatic breast cancer population. We also paused the development of our preclinical product candidate, ARX822. As part of the reprioritization and reconsideration in the first quarter of 2023, we are focusing on strengthening our current partnerships, while pursuing internal development of ARX788. In parallel, we are internally developing our earlier stage programs where we believe we offer a first-in-class or best-in-class approach. Finally, as part of this strategic update, we streamlined our organization with a reduction in force in the fourth quarter of 2022 to improve efficiency and to reprioritize our development pipeline to focus on oncology assets with the greatest potential and strong competitive profiles.

Because we have limited financial and managerial resources, we focus on specific product candidates, indications and development programs. We may also conduct several clinical trials for our product candidates in parallel over the next several years, which may make our decision as to which product candidates to focus on more difficult. For example, we are currently conducting a Phase 1 clinical trial for the evaluation of the safety of ARX517. Further, we are investing in preclinical studies for ARX305 and ARX102. As a result, we may forgo or delay pursuit of opportunities with other product candidates or other indications that could have had greater commercial potential or likelihood of success. Our resource allocation decisions may cause us to fail to capitalize on viable commercial products or profitable market opportunities. Our spending on current and future research and development programs and product candidates for specific indications may not yield any commercially viable products. If we do not accurately evaluate the commercial potential or target market for a particular product candidate, we may relinquish valuable rights to that product candidate through future collaborations, licenses and other similar arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to such product candidate.

Our business is highly dependent on our product candidates, and we must complete additional clinical testing before we can seek regulatory approval and begin commercialization of any of our product candidates for any indication. If we are unable to obtain regulatory approval for, and successfully commercialize, our product candidates, our business may be materially harmed and such failure may affect the viability of our other product candidates.

Our product candidates may not proceed in preclinical or through clinical development or achieve regulatory approval. The process for obtaining marketing approval for any product candidate is very long and risky and there will be significant challenges for us to address in order to obtain marketing approval as planned or, if at all.

The results obtained in our current clinical trials or future clinical trials may not be sufficient to obtain regulatory approval. In addition, because our current and future product candidates are based or will be based on our synthetic amino acid, or SAA, technology, if any of our product candidates encounter safety or efficacy problems, developmental delays, regulatory issues, or other problems, our development plans and business related to our other current or future product candidates could be significantly harmed. In addition, our most advanced internal product candidates in our antibody-drug conjugates, or ADC, franchise rely on AS269, our proprietary cytotoxic payload, meaning that a toxicity, manufacturing or other issue with AS269 could negatively impact these other product candidates, which would harm our business. A failure of any of our product candidates may affect the ability to obtain regulatory approval to continue or conduct clinical programs for our other or future product candidates. Moreover, anti-tumor activity may be different in each of the different tumor types we plan on evaluating in our clinical trials. As a consequence, we may have to interact with the United States Food and Drug Administration, or FDA, as well as other regulatory authorities to reach agreement on defining the optimal patient population, study design and size in order to obtain regulatory approval, any of which may require additional resources and delay the timing of our clinical trials and ultimately the approval, if any, of any of our product candidates. Further, competitors who are developing products with similar technology may experience problems with their products that could become, or be perceived to be, problems with our product candidates.

Preclinical and clinical development is a lengthy, expensive and uncertain process. The results of preclinical studies and early clinical trials are not always predictive of future results. If our preclinical studies and clinical trials are not sufficient to support regulatory approval of any of our product candidates, we may incur additional costs or experience delays in completing, or ultimately be unable to complete, the development of such product candidate.

The research and development of drugs and biological products is extremely risky. Only a small percentage of product candidates that enter the development process ever receive marketing approval. Before obtaining marketing approval from regulatory authorities for the sale of our product candidates, we must conduct extensive clinical trials to demonstrate the safety and efficacy of the product candidates in humans. Clinical testing is expensive, can take many years to complete and its outcome is uncertain. We may face unforeseen challenges in our product candidate development strategy, and we may not ultimately be successful in our current and future clinical trials and our product candidates may not be able to receive regulatory approval. The results of preclinical studies and early clinical trials of our product candidates and other products, even those with the same or similar mechanisms of action, may not be predictive of the results of later-stage clinical trials. For example, it is not uncommon for product candidates to exhibit unforeseen safety or efficacy issues when tested in humans despite promising results in preclinical animal models. In particular, while we have conducted and seen promising results in preclinical studies of our product candidates, we do not know how any of these product candidates will perform in clinical trials.

Future results of preclinical and clinical testing of our product candidates are also less certain due to the novel and relatively untested nature of our approach in engineering and developing engineered precision biologics, or EPBs, and incorporating SAAs into proteins. In general, clinical trial failure may result from a multitude of factors including flaws in study design, dose selection, patient enrollment criteria and failure to demonstrate favorable safety or efficacy traits. We may also experience issues related to product formulation changes, which we have made with respect to our product candidates both before and during clinical development. As such, failure in clinical trials can occur at any stage of testing. A number of companies in the biologics industry have suffered setbacks in the advancement of clinical trials due to lack of efficacy or adverse safety profiles, notwithstanding promising results in earlier trials.

Additionally, some of our ongoing and future clinical trials may be open-label in study design and may be conducted at a limited number of clinical sites on a limited number of patients. An “open-label” clinical trial is one where both the patient and investigator know whether the patient is receiving the investigational product candidate or either an existing approved drug or placebo. Most typically, open-label clinical trials test only the investigational product candidate and sometimes may do so at different dose levels. Open-label clinical trials are subject to various limitations that may exaggerate any therapeutic effect as patients in open-label clinical trials are aware when they are receiving treatment and, thus, the results may not be predictive of future clinical trial results.

Prior to obtaining approval to commercialize any product candidate in the United States, or internationally, we must demonstrate with substantial evidence from adequate and well-controlled clinical trials, and to the satisfaction of the FDA, National Medical Products Administration, or NMPA, European Medicines Agency, or EMA, or comparable foreign regulatory authorities, that such product candidate is safe and effective for its intended uses. Results from preclinical studies and clinical trials can be interpreted in different ways. Even if we believe that the preclinical or clinical data for our product candidates are promising, such data may not be sufficient to support approval by the FDA, NMPA, EMA or comparable regulatory authorities. The FDA or other regulatory authorities may also require us to conduct additional preclinical studies or clinical trials for our product candidates either prior to or post-approval, or they may object to elements of our clinical development program, requiring their alteration.

If the results of our clinical trials are inconclusive or if there are safety concerns, adverse events associated with our product candidates or clinical holds placed by regulatory authorities on any of our product candidates, we may:

- incur unplanned costs;
- be delayed in or prevented from continuing clinical development and obtaining marketing approval for our product candidates;
- obtain approval for indications or patient populations that are not as broad as intended or desired;
- obtain approval with labeling that includes significant use or distribution restrictions or safety warnings, including boxed warnings or contraindications;
- be subject to changes or limitations in the way the product is administered;
- be required to perform additional preclinical studies or clinical trials to support approval or be subject to additional post-marketing testing requirements;
- have regulatory authorities withdraw their approval of the product, if granted, or impose restrictions on its distribution in the form of a Risk Evaluation and Mitigation Strategy, or REMS;
- become subject to litigation;
- be forced to terminate clinical development of any of our product candidates; or
- experience damage to our reputation.

If we are required to conduct additional clinical trials or other testing of our product candidates beyond those that we currently contemplate, if we are unable to successfully complete clinical trials of our product candidates or other testing, if the results of these trials or tests are not positive or are not as positive as we expect or if there are safety concerns, our business and results of operations will likely be adversely affected and we may incur significant additional costs.

In addition, even if the clinical trials are successfully completed, preclinical and clinical data are often susceptible to varying interpretations and analyses, and the FDA, NMPA, EMA or comparable foreign regulatory authorities may not interpret the results as we do, and more clinical trials could be required before we submit our product candidates for approval. To the extent that the results of the clinical trials are not satisfactory to the FDA, NMPA, EMA or comparable foreign regulatory authorities for support of a marketing application, approval of our product candidates may be significantly delayed, or we may be required to expend significant additional resources, which may not be available to us, to conduct additional clinical trials in support of potential approval of our product candidates.

Our product candidates are based on novel technologies, making it difficult to predict the timing, results and cost of product candidate development and likelihood of obtaining regulatory approval.

We have concentrated our research and development efforts on product candidates using our platform technologies, and our future success depends on the successful development of this approach. We have not yet succeeded and may not succeed in demonstrating efficacy and safety for any product candidates based on our platform technologies, and use of our platform technologies may not ever result in marketable therapies. In particular, while we believe that our site-specific incorporation of SAAs into proteins may be capable of overcoming certain challenges faced by traditional ADC approaches, our technologies may not result in the intended benefits or may result in unforeseen negative consequences, particularly because there is limited experience in the field with this approach to engineering bio-conjugates.

In addition, the clinical trial requirements of the FDA, NMPA, EMA and comparable regulatory agencies and the criteria these regulators use to determine the safety and efficacy of a product candidate vary substantially according to the type, complexity, novelty, intended use and market of the potential products. The regulatory approval process for novel product candidates such as ours can be more expensive and take longer than for other, better known or extensively studied approaches.

The ADC and immuno-oncology fields are also rapidly evolving and as competitors use or develop alternative technologies, any failures of related product candidates could adversely impact our programs. For example, other companies are developing novel conjugation approaches to ADCs. Regardless of our belief that our approach of EPBs has advantages over conventional biologics and bio-conjugates, issues encountered with other programs could create a negative perception of or increase scrutiny for our platform technologies and product candidates.

As an organization, we are in the process of conducting preclinical and Phase 1 clinical trials, have never conducted later-stage clinical trials or submitted a biologics license application, or BLA, and may be unable to do so for any of our product candidates.

We are undertaking development efforts for our product candidates, and we will need to successfully complete clinical development, including later-stage and pivotal clinical trials, in order to obtain FDA, NMPA, EMA or comparable regulatory authority approval to market our current or any future product candidates. Carrying out later-stage clinical trials and the submission of a successful BLA is a complicated process. As an organization, we are in the process of conducting preclinical and Phase 1 clinical trials and have not yet conducted any, and have relied, and will continue to rely, on collaboration partners to conduct later stage or potentially pivotal clinical trials for our current and future product candidates. We have limited experience as a company in preparing, submitting and prosecuting regulatory filings and have not previously submitted a BLA or other comparable foreign regulatory submission for any product candidate. We also plan to conduct a number of clinical trials for multiple product candidates in parallel over the next several years. This may be a difficult process to manage with our limited resources. In addition, we have had limited interactions with the FDA and cannot be certain how many clinical trials of our product candidates will be required or how such trials will have to be designed. Consequently, we may be unable to successfully and efficiently execute and complete necessary clinical trials in a way that leads to regulatory submission and approval of any of our product candidates. We may require more time and incur greater costs than our competitors and may not succeed in obtaining regulatory approvals of product candidates that we develop. Failure to commence or complete, or delays in, our planned clinical trials, could prevent us from or delay us in submitting BLAs for and commercializing our product candidates.

We may encounter substantial delays in initiating or completing our clinical trials.

Clinical trials may not be initiated or completed on schedule, if at all. For example, we cannot begin Phase 1 clinical trials until we complete certain preclinical development activities and submit and receive authorization to proceed under IND applications and the timing and success of these events are uncertain. We may experience delays in obtaining the FDA's authorization to initiate clinical trials under future INDs. Even after we are authorized to proceed with clinical trials, numerous events could prevent successful or timely completion of clinical development, including:

- delays in reaching a consensus with regulatory authorities on trial design;
- delays in reaching agreement or failing to agree on acceptable terms with prospective contract research organizations, or CROs, and clinical trial sites;
- delays in opening sites, including delays in obtaining required approvals from institutional review boards, or IRBs, and recruiting suitable patients to participate in our clinical trials;
- delays in enrolling patients in our clinical trials;
- failure by our CROs, other third parties or us to adhere to the trial protocol or applicable regulatory requirements, including the FDA's good clinical practices, or GCPs, or applicable regulatory requirements in other countries;
- regulatory authorities finding deficiencies in the manufacturing processes or facilities of third-party manufacturers with which we or any of our potential future collaborators contract for clinical supplies;
- delays in the testing, validation, manufacturing and delivery of our product candidates to the treatment sites, including due to a facility manufacturing any of our product candidates or any of their components being ordered by the FDA, NMPA, EMA or comparable regulatory authorities to temporarily or permanently shut down due to violations of current good manufacturing practices, or cGMP, regulations or other applicable requirements, or infections or cross-contaminations of product candidates in the manufacturing process;
- imposition of a clinical hold by IRBs or regulatory authorities as a result of a serious adverse event, or SAE, concerns with a class of product candidates, after an inspection of our clinical trial operations or trial sites, or for other reasons;
- suspensions or terminations by us, the IRBs or the institutions at which such trials are being conducted, by the Safety Review Committee or Data Safety Monitoring Board, for such trial or by regulatory authorities due to a number of factors, including those described above;
- patients not completing participation in a trial, returning for post-treatment follow-up or otherwise failing to adhere to clinical trial protocols;
- lack of adequate funding; or
- changes in regulatory requirements and guidance that require amending or submitting new clinical protocols.

In addition, the ongoing COVID-19 pandemic, and the measures taken by governmental authorities to slow its spread, and the ongoing conflict between Ukraine and Russia could disrupt the supply chain and the manufacture or shipment of drug substances and finished drug products for our product candidates for use in our research and clinical trials, delay, limit or prevent our employees and CROs from continuing research and development activities, impede the ability of patients to enroll or continue in clinical trials, or impede testing, monitoring, data collection and analysis or other related activities, any of which could delay our clinical trials and increase our development costs, and have a material adverse effect on our business, financial condition and results of operations. For example, the COVID-19 pandemic has impacted our clinical trial sites in the United States and Australia, with some sites temporarily suspending or slowing enrollment due to quarantines, travel limitations, site personnel shortages or patients' fear of contracting COVID-19.

Any inability to timely initiate and successfully complete clinical trials could result in additional costs to us or impair our ability to achieve regulatory and commercialization milestones. Clinical trial delays could also shorten any periods during which we may have the exclusive right to commercialize our product candidates, if approved, or allow our competitors to bring comparable drugs to market before we do, which could impair our ability to successfully commercialize our product candidates and may harm our business, financial condition, results of operations and prospects.

If we experience delays or difficulties enrolling patients in our clinical trials, our research and development efforts and business, financial condition and results of operations could be materially adversely affected.

Successful and timely completion of clinical trials will require that we identify, qualify and enroll a sufficient number of patients. These trials and other trials we conduct may be subject to delays as a result of patient enrollment taking longer than anticipated, patient withdrawal or adverse events, which may be as serious as death. Delays in enrolling patients in these trials would adversely impact our overall clinical development strategy for our product candidates and delay our ability to seek regulatory approval.

Our clinical trials compete with other clinical trials that are in the same therapeutic areas as our product candidates, and this competition will reduce the number and types of patients available to us, because some patients who might have opted to enroll in our trials may instead opt to enroll in trials being conducted by others. For example, we estimate that there are approximately 1.4 million annual new cases of prostate cancer worldwide. We have competed, and expect to continue to compete, with other clinical trials that involve product candidates targeting prostate cancer.

Because the number of qualified clinical investigators and clinical trial sites is limited, we expect to conduct some of our clinical trials at the same clinical trial sites that some of our competitors use, which will reduce the number of patients who are available for our clinical trials at such clinical trial sites. Moreover, because certain of our product candidates represent a departure from more commonly used methods for cancer treatment and because certain of our product candidates have not been tested in humans before, potential patients and their doctors may be inclined to use conventional therapies, such as other available therapies, rather than enroll patients in any future clinical trial.

In addition to the potentially small populations, the eligibility criteria of our planned clinical trials will further limit the pool of available study participants as we will require that patients have specific characteristics. Additionally, the process of finding and diagnosing patients may prove costly. We also may not be able to identify, recruit and enroll a sufficient number of patients to complete our clinical trials because of the perceived risks and benefits of the product candidate under study, the availability and efficacy of competing therapies and clinical trials, the proximity and availability of clinical trial sites for prospective patients, the availability of genetic sequencing information for patient tumors so that we can identify patients with the targeted genetic mutations, and the patient referral practices of physicians. If patients are unwilling to participate in our studies for any reason, the timeline for recruiting patients, conducting studies and obtaining regulatory approval of potential products may be delayed.

Patient enrollment depends on many factors, including:

- the size and nature of the patient population;
- the severity of the disease under investigation;
- eligibility criteria for the trial;
- the proximity of patients to clinical sites;
- the design of the clinical protocol;
- the ability to obtain and maintain patient consents;
- the ability to recruit clinical trial investigators with the appropriate competencies and experience;
- the risk that patients enrolled in clinical trials will drop out of the trials before the administration of our product candidates or trial completion;

- reporting of the preliminary results of our clinical trials;
- the number of competing clinical trials;
- the availability of new drugs approved for the indication the clinical trial is investigating;
- clinicians' and patients' perceptions as to the potential benefit-risk ratio of the drug being studied in relation to other available therapies;
- lack of safety and efficacy data of our product candidates;
- competing clinical trials for qualified patients; and
- other factors we may not be able to control.

In addition, the COVID-19 pandemic has impacted clinical trials broadly, including our own, with some sites temporarily suspending or slowing enrollment due to quarantines, travel limitations, site personnel shortages or patients unwilling to enroll out of fear of contracting COVID-19. Enrollment and retention of patients in clinical trials could also be disrupted by geopolitical events, including civil or political unrest (such as the ongoing conflict between Ukraine and Russia), terrorism, insurrection or war, man-made or natural disasters, or public health pandemics or epidemics or other business interruptions, including bank failures, the COVID-19 pandemic and future outbreaks of disease. These factors may make it difficult for us to enroll enough patients to complete our clinical trials in a timely and cost-effective manner. Delays in the completion of any clinical trial of our product candidates will increase our costs, slow down our product candidate development and approval process and delay or potentially jeopardize our ability to commence product sales and generate revenue. In addition, some of the factors that cause, or lead to, a delay in the commencement or completion of clinical trials may also ultimately lead to the denial of regulatory approval of our product candidates.

SAEs, undesirable side effects or other unexpected properties of our product candidates may be identified during development or after approval, which could lead to the discontinuation of our clinical development programs, clinical holds by regulatory authorities, refusal by regulatory authorities to approve our product candidates or, if discovered following marketing approval, revocation of marketing authorizations or limitations on the use of our product candidates thereby limiting the commercial potential of such product candidate.

To date, we have only tested our product candidates in a limited number of cancer patients and these clinical trial participants have only been observed for a limited period of time after dosing. As we continue developing our product candidates and initiate clinical trials of our current and future product candidates, SAEs, undesirable side effects, relapse of disease or unexpected characteristics including but not limited to death and ocular toxicity, will likely emerge and may cause us to abandon these product candidates or limit their development to more narrow uses or subpopulations in which the SAEs, undesirable side effects or other characteristics are less prevalent, less severe or more acceptable from a risk-benefit perspective or in which efficacy is more pronounced or durable. For example, the general goal of ADC approaches is to deliver a toxic payload to a tumor site to kill the cancer cells, but the unintended exposure of healthy cells to the cytotoxic payload has resulted in numerous ADC candidates failing in development due to safety issues, which can be as serious as death, and has limited the therapeutic window of approved ADC therapies, and our ADC candidates may suffer from similar safety issues. Should we observe unexpected types or levels of SAEs in our clinical trials or identify other undesirable side effects or other unexpected safety findings, our trials could be delayed or even stopped, and our development programs may be halted entirely. Adverse events, even if non-serious, may harm our ability to obtain marketing approvals for our current and any future product candidates, or, if approved, to achieve market adoption.

Even if our product candidates initially show promise in early clinical trials, the side effects of biological products are frequently only detectable after they are tested in larger, longer and more extensive clinical trials or, in some cases, after they are made available to patients on a commercial scale after approval. Sometimes, it can be difficult to determine if the SAEs or unexpected side effects were caused by the product candidate or another factor, especially in oncology subjects who may suffer from other medical conditions and be taking other medications. For example, treatment of cancer patients with our immuno-oncology, or IO, product candidates may be in combination with other cancer drugs, such as other immuno-oncology agents, monoclonal antibodies or other protein-based drugs or small molecule anti-cancer agents such as targeted agents or chemotherapy, which can cause side effects or adverse events that are unrelated to our product candidate but may still impact the success of our clinical trials. Additionally, the inclusion of critically ill patients in our clinical trials may result in deaths or other adverse medical events due to other therapies or medications that such patients may be using or other underlying conditions. As described above, any of these events could prevent us from obtaining regulatory approval or achieving or maintaining market acceptance of our product candidates and impair our ability to commercialize our products.

If SAEs or unexpected side effects, including but not limited to deaths or ocular toxicities, are identified during development or after approval and are determined to be attributed to our product candidate, we may be required to develop a REMS plan to ensure that the benefits of treatment with such product candidate outweigh the risks, which may include, among other things, a medication guide, communication plan to healthcare practitioners or additional elements to assure safe use, such as patient education, extensive patient monitoring through registries or restricted distribution methods. Product-related side effects could also result in potential product liability claims. Any of these occurrences may harm our business, financial condition and prospects significantly.

In addition, if one or more of our product candidates receives marketing approval, and we or others later identify undesirable side effects caused by such products, or any other similar biologics, after such approval, a number of potentially significant negative consequences could result, including:

- regulatory authorities may suspend, withdraw or limit approvals of such product;
- regulatory authorities may require additional warnings on the label, including a “boxed” warning or contraindication, or issue safety alerts, Dear Healthcare Provider letters, press releases or other communications containing warnings or other safety information about the product;
- regulatory authorities may require a REMS plan to mitigate risks;
- we may be required to change the way a product is distributed or administered, conduct additional clinical trials, or change the labeling of the product;
- the product may become less competitive, and our reputation may suffer;
- we may decide to remove the product from the marketplace; and
- we may be subject to regulatory investigations and government enforcement actions, including fines, injunctions or the imposition of civil or criminal penalties.

Interim, topline and preliminary data from our preclinical studies and clinical trials may change as more data become available and are subject to audit and verification procedures that could result in material changes in the final data.

We have disclosed and intend to publicly disclose from time to time in the future, interim, topline or preliminary data from our preclinical studies and clinical trials, which is based on a preliminary analysis of then-available data, and the results and related findings and conclusions are subject to change as more data become available. We may also announce topline data following the completion of a preclinical study or clinical trial, which may be subject to change following a more comprehensive review of the data related to the particular study or trial. We also make assumptions, estimations, calculations and conclusions as part of our analyses of data, and we may not have received or had the opportunity to fully and carefully evaluate all data. As a result, the interim, topline or preliminary results that we report may differ from future results of the same studies, or different conclusions or considerations may qualify such results, once additional data have been received and fully evaluated. Top line data also remain subject to audit and verification procedures that may result in the final data being materially different from the preliminary data we previously published. As a result, interim, topline and preliminary data should be viewed with caution until the final data are available. Adverse differences between previous preliminary or interim data and future interim or final data could significantly harm our business prospects.

From time to time, we may also disclose interim data from our clinical trials. Interim data from clinical trials that we may complete are subject to the risk that one or more of the clinical outcomes may materially change as patient enrollment continues and more patient data become available or as patients from our clinical trials continue other treatments for their disease. Adverse differences between preliminary or interim data and final data could significantly harm our business prospects. Further, disclosure of interim data by us, our collaboration partners, or by our competitors could result in volatility in the price of our ADSs.

Further, others, including regulatory agencies, may not accept or agree with our assumptions, estimates, calculations, conclusions or analyses or may interpret or weigh the importance of data differently, which could impact the value of the particular program, the approvability or commercialization of the particular product candidate or product, our company in general and our ADSs. In addition, the information we choose to publicly disclose regarding a particular study or clinical trial is based on what is typically extensive information, and you or others may not agree with what we determine to be material or otherwise appropriate information to include in our disclosure, and any information we determine not to disclose may ultimately be deemed significant with respect to future decisions, conclusions, views, activities or otherwise regarding a particular product candidate or our business. If the interim, topline, or preliminary data that we report differ from future or more comprehensive data, or if others, including regulatory authorities, disagree with the conclusions reached, our ability to obtain approval for and commercialize our product candidates, our business, operating results, prospects or financial condition may be harmed.

We may not be able to submit INDs or IND amendments to commence additional clinical trials on the timelines we expect, and even if we are able to, the FDA may not permit us to proceed.

We may not be able to submit future INDs for our product candidates on the timelines we expect. For example, we may experience manufacturing delays or other delays with IND-enabling studies. Moreover, submission of an IND may not result in the FDA allowing further clinical trials to begin, and, once begun, issues may arise that suspend or terminate clinical trials. Additionally, even if such regulatory authorities agree with the design and implementation of the clinical trials set forth in an IND, such regulatory authorities may change their requirements in the future. These considerations also apply to new clinical trials we may submit as amendments to existing INDs or to a new IND. Any failure to submit INDs on the timelines we expect or to obtain regulatory approvals for our trials may prevent us from completing our clinical trials or commercializing our products on a timely basis, if at all.

We may investigate one or more of our product candidates in combination with other therapies, which exposes us to additional risks.

We may investigate one or more of our product candidates in combination with one or more other approved or unapproved therapies to treat cancer or other diseases. Even if any product candidate we develop were to receive marketing approval or be commercialized for use in combination with other existing therapies, we would continue to be subject to the risks that the FDA or comparable foreign regulatory authorities outside of the United States could revoke approval of the therapy used in combination with our product or that safety, efficacy, manufacturing or supply issues could arise with any of those existing therapies. If the therapies we use in combination with our product candidates are replaced as the standard of care for the indications we choose for any of our product candidates, the FDA or comparable foreign regulatory authorities may require us to conduct additional clinical trials. The occurrence of any of these risks could result in our own products, if approved, being removed from the market or being less successful commercially.

We also may choose to evaluate our current product candidates or any other future product candidates in combination with one or more cancer therapies that have not yet been approved for marketing by the FDA or comparable foreign regulatory authorities. We will not be able to market and sell our current product candidates or any product candidate we develop in combination with an unapproved cancer therapy for a combination indication if that unapproved therapy does not ultimately obtain marketing approval either alone or in combination with our product. In addition, unapproved cancer therapies face the same risks described with respect to our product candidates currently in development and clinical trials, including the potential for serious adverse effects, delay in their clinical trials and lack of FDA approval.

If the FDA or comparable foreign regulatory authorities do not approve these other products or revoke their approval of, or if safety, efficacy, quality, manufacturing or supply issues arise with, the products we choose to evaluate in combination with our product candidate we develop, we may be unable to obtain approval of or market such combination therapy.

We may seek Breakthrough Therapy or Fast Track designations by the FDA for one or more of our product candidates, but we may not receive such designations, and even if we do, such designations may not lead to a faster development or regulatory review or approval process and it does not increase the likelihood that our product candidates will receive marketing approval.

We may seek Fast Track and/or Breakthrough Therapy designations for one or more of our product candidates. If a drug or biologic is intended for the treatment of a serious or life-threatening condition and clinical or preclinical data demonstrate the potential to address unmet medical needs for this condition, the product candidate may be eligible for Fast Track designation. The benefits of Fast Track designation include more frequent interactions between FDA and the sponsor of the trial to discuss the product candidate's development plan and extent of safety data needed to support approval and use of biomarkers. Product candidates that have been designated as Fast Track are also eligible for rolling review, which means that a sponsor can submit completed sections of its BLA for review by FDA, rather than waiting until every section of the BLA is completed before the entire application can be reviewed. BLA review usually does not begin until the entire application has been submitted to the FDA.

A Breakthrough Therapy is defined as a drug or biologic that is intended, alone or in combination with one or more other drugs or biologics, to treat a serious or life-threatening disease or condition and preliminary clinical evidence indicates that the product candidate may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. A product candidate designated as a Breakthrough Therapy by the FDA may be eligible for all features of Fast Track designation, intensive guidance on an efficient product development program, beginning as early as Phase 1, and organizational commitment involving senior managers at the FDA.

Product candidates designated as Fast Track and Breakthrough Therapy by the FDA may also be eligible for other expedited approval programs, including accelerated approval and priority review, but such designation does not assure any such qualification or ultimate marketing approval by the FDA. The FDA has broad discretion whether or not to grant these designations, so even if we believe a particular product candidate is eligible for a designation, the FDA may not decide to grant it. Even if designated, we may not experience a faster development process, review or approval compared to non-expedited FDA review procedures. In addition, the FDA may withdraw Fast Track designation or Breakthrough Therapy designation if it believes that the designation is no longer supported by emerging data or the product development program is no longer being pursued.

We may seek orphan drug designations by the FDA for certain of our product candidates, but we may be unable to obtain such designations or maintain or ultimately realize the potential benefits of orphan drug designation.

We may seek orphan drug designation for certain of our product candidates. The FDA grants orphan designation to drugs or biologics that are intended to treat a rare disease or condition with fewer than 200,000 patients in the United States or that affects 200,000 or more persons in the United States but where there is no reasonable expectation for a sponsor to recover the costs of developing and marketing the drug or biologic in the United States. Orphan drug designation must be requested before submitting an NDA or BLA. In the United States, orphan drug designation entitles a party to financial incentives such as opportunities for grant funding towards clinical trial costs, tax advantages, and application fee waivers. After the FDA grants orphan drug designation, the generic identity of the drug or biologic and its potential orphan use are disclosed publicly by the FDA. However, orphan drug designation neither shortens the development time nor regulatory review time of a product candidate nor gives the candidate any advantage in the regulatory review or approval process.

In addition, if a product that has orphan designation subsequently receives the first FDA approval for a particular active ingredient for the indication for which it has orphan designation, the product is entitled to orphan product exclusivity, which means the FDA may not approve any other application to market the same drug or biologic for the same indication for a period of seven years, except in limited circumstances, such as a showing of clinical superiority over the product with orphan exclusivity or where the manufacturer is unable to assure sufficient product quantity to meet the needs of patients for which the product was designated. As a result, even if one of our product candidates receives orphan exclusivity, the FDA can still approve other drugs and biologics that have a different active ingredient for use in treating the same indication or disease. Furthermore, the FDA can waive orphan exclusivity if we are unable to manufacture sufficient supply of our product.

We may seek orphan drug designation for certain of our product candidates in orphan indications in which there is a medically plausible basis for the use of these products. Even if we obtain orphan drug designation, exclusive marketing rights in the United States may also be unavailable if we or our collaborators seek approval for an indication broader than the orphan designated indication and may be lost if the FDA later determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantities of the product to meet the needs of patients with the rare disease or condition. In addition, even if we seek orphan drug designation for certain of our other product candidates, we may never receive such designations. Even if we obtain orphan drug designation, we may not be the first to obtain marketing approval for any particular orphan indication due to the uncertainties associated with developing pharmaceutical products. Further, even if we obtain orphan exclusivity for a product candidate, that exclusivity may not effectively protect the product from competition because different drugs or biologics can be approved for the same condition.

The FDA may further reevaluate the Orphan Drug Act and its regulations and policies. We do not know if, when, or how the FDA may change the orphan drug regulations and policies in the future, and it is uncertain how any changes might affect our business. Depending on what changes the FDA may make to its orphan drug regulations and policies, our business could be adversely impacted.

We may seek accelerated approval by the FDA for certain of our product candidates, but the FDA may not agree that the accelerated approval pathway is appropriate, which may prolong development and delay our projected commercialization plans.

We may seek approval of certain of our product candidates using the FDA's accelerated approval pathway. Accelerated approval requires the data to indicate the product candidate has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or an effect on a clinical endpoint that can be measured earlier than an effect on irreversible morbidity or mortality that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments. However, it is possible that at the time of a BLA submission, a given product candidate would not be eligible for accelerated approval or the FDA could determine that accelerated approval is not warranted. In particular, it is difficult to predict whether accelerated approval will be possible for ARX517 at the time we expect to submit a BLA. If data from our initial Phase 1a clinical trials do not provide evidence sufficient for accelerated approval, additional clinical testing would be required to support approval. While we intend to initiate randomized Phase 1b/2 clinical trials for ARX517 regardless, if we were unable to obtain accelerated approval based on the results of our Phase 1a clinical trial, it could significantly delay the approval of, and our ability to commercialize, ARX517.

As a condition of accelerated approval, the FDA requires that a sponsor of a product receiving accelerated approval perform adequate and well-controlled post-marketing clinical trials. These confirmatory trials must be completed with due diligence. In addition, the FDA currently requires as a condition for accelerated approval pre-approval of promotional materials, which could adversely impact the timing of the commercial launch of the product.

We currently conduct and may in the future conduct clinical trials for our product candidates outside the United States, and the FDA, NMPA, EMA or comparable foreign regulatory authorities may not accept data from such trials.

We are conducting and plan to conduct one or more future clinical trials of our product candidates outside the United States, including in Europe, Australia and China. The acceptance of trial data from clinical trials conducted outside the United States or another jurisdiction by the FDA or comparable foreign regulatory authorities may be subject to certain conditions or may not be accepted at all. In cases where data from clinical trials conducted outside the United States are intended to serve as the sole basis for marketing approval in the United States, the FDA will generally not approve the application on the basis of foreign data alone unless (i) the data are applicable to the United States population and United States medical practice; (ii) the trials were performed by clinical investigators of recognized competence and (iii) the data may be considered valid without the need for an on-site inspection by the FDA or, if the FDA considers such an inspection to be necessary, the FDA is able to validate the data through an on-site inspection or other appropriate means. Additionally, the FDA's clinical trial requirements, including sufficient size of patient populations and statistical powering, must be met. Many foreign regulatory bodies have similar approval requirements. In addition, such foreign trials would be subject to the applicable local laws of the foreign jurisdictions where the trials are conducted. The FDA, NMPA, EMA or any comparable foreign regulatory authority may not accept data from trials conducted outside of the United States or the applicable jurisdiction. If the FDA, NMPA, EMA or any comparable regulatory authority does not accept such data, it would result in the need for additional trials, which would be costly and time-consuming and delay aspects of our business plan, and which may result in our product candidates not receiving approval or clearance for commercialization in the applicable jurisdiction.

Our product candidates must meet extensive regulatory requirements before they can be commercialized and any regulatory approval may contain limitations or conditions that require substantial additional development expenses or limit our ability to successfully commercialize the product.

Our product candidates and the activities associated with their clinical development and commercialization, including their design, testing, manufacture, safety, efficacy, labeling, storage, record-keeping, approval, advertising, promotion, import, export, marketing and distribution are subject to extensive regulation by the FDA in the United States and by comparable foreign regulatory authorities in foreign markets. In the United States, we are not permitted to market our product candidates until we receive regulatory approval from the FDA. Whether the results from our ongoing clinical trials and other trials will suffice to obtain approval will be a review issue and the FDA may not grant approval and may require that we conduct one or more controlled clinical trials to obtain approval. Securing regulatory approval requires the submission of information about the product manufacturing process to, and inspection of manufacturing facilities by, the relevant regulatory authority. The process of obtaining regulatory approval is expensive, often takes many years following the commencement of clinical trials and can vary substantially based upon the type, complexity and novelty of the product candidates involved, as well as the target indications and patient population. Despite the time and expense invested in clinical development of product candidates, regulatory approval is never guaranteed.

To date, we have not submitted a BLA or other marketing authorization application to the FDA or similar drug approval submissions to comparable foreign regulatory authorities for any product candidate. Prior to obtaining approval to commercialize a product candidate in the United States or abroad, we or our potential future collaborators must demonstrate with substantial evidence from adequate and well-controlled clinical trials, and to the satisfaction of the FDA, NMPA, EMA or comparable regulatory authorities, that such product candidates are safe and effective for their intended uses. Even if we believe the preclinical or clinical data for our product candidates are promising, such data may not be sufficient to support approval by the FDA, NMPA, EMA or comparable regulatory authorities. In particular, because we are seeking to identify and develop product candidates using new technologies, there is heightened risk that the FDA, NMPA, EMA or comparable regulatory authorities may impose additional requirements prior to granting marketing approval, including enhanced safety studies or monitoring. Furthermore, as more product candidates within a particular class of products proceed through clinical development to regulatory review and approval, the amount and type of clinical data that may be required by regulatory authorities may increase or change.

The FDA, NMPA, EMA or comparable regulatory authorities can delay, limit or deny approval of a product candidate for many reasons, including:

- such authorities may disagree with the design or implementation of our clinical trials;
- negative or ambiguous results from our clinical trials or results may not meet the level of statistical significance required by the FDA, NMPA, EMA or comparable regulatory authorities for approval;
- serious and unexpected product-related side effects may be experienced by participants in our clinical trials or by individuals using biological products similar to our product candidates;
- the population studied in the clinical trial may not be sufficiently broad or representative to assure safety in the full population for which we seek approval;
- such authorities may not accept clinical data from trials which are conducted at clinical facilities or in countries where the standard of care is potentially different from that of the United States;
- we may be unable to demonstrate that a product candidate's clinical and other benefits outweigh its safety risks or that a product candidate is safe and effective for its proposed indication;
- such authorities may disagree with our interpretation of data from preclinical studies or clinical trials;
- such authorities may not agree that the data collected from clinical trials of our product candidates are acceptable or sufficient to support the submission of an application for regulatory approval or other submissions or to obtain regulatory approval in the United States or elsewhere, including due to clinical trial issues encountered as a result of COVID-19 pandemic, and such authorities may impose requirements for additional preclinical studies or clinical trials;

- such authorities may disagree regarding the formulation, labeling and/or the specifications of our product candidates;
- approval may be granted only for indications that are significantly more limited than what we apply for and/or with other significant restrictions on distribution and use;
- such authorities may fail to approve any required companion diagnostics to be used with our product candidates;
- such authorities may find deficiencies in the manufacturing processes or facilities of our third-party manufacturers with which we or any of our potential future collaborators contract for clinical and commercial supplies; or
- the approval policies or regulations of such authorities may significantly change in a manner rendering our or any of our potential future collaborators' clinical data insufficient for approval.

With respect to foreign markets, approval procedures vary among countries and, in addition to the foregoing risks, may involve additional product testing, administrative review periods and agreements with pricing authorities. In addition, events raising questions about the safety of certain marketed pharmaceuticals may result in increased cautiousness by the FDA, NMPA, EMA or comparable regulatory authorities in reviewing new products based on safety, efficacy or other regulatory considerations and may result in significant delays in obtaining regulatory approvals.

Even if we eventually complete clinical trials and receive approval to commercialize our product candidates, the FDA, NMPA, EMA or comparable regulatory authority may grant approval contingent on the performance of costly additional clinical trials, including Phase 4 clinical trials, and/or the implementation of a REMS. The FDA, NMPA, EMA or comparable regulatory authority also may approve a product candidate for a more limited indication or patient population than we originally requested or may not approve the labeling that we believe is necessary or desirable for the successful commercialization of a product. Manufacturers of our products and manufacturers' facilities are also required to comply with cGMP regulations, which include requirements related to quality control and quality assurance, as well as the corresponding maintenance of records and documentation. Further, regulatory authorities must approve these manufacturing facilities before they can be used to manufacture our products, and these facilities are subject to continual review and periodic inspections by the FDA, NMPA, EMA or comparable regulatory authorities for compliance with cGMP regulations.

Any delay in obtaining, or inability to obtain, applicable regulatory approval would delay or prevent commercialization of that product candidate and would materially and adversely impact our business and prospects.

Even if we obtain regulatory approval for our product candidates, they will remain subject to ongoing regulatory oversight. Additionally, our product candidates, if approved, could be subject to labeling and other restrictions on marketing or withdrawal from the market, and we may be subject to penalties if we fail to comply with regulatory requirements or if we experience unanticipated problems with our product candidates, when and if any of them are approved.

Even if we obtain regulatory approval for any of our product candidates, they will be subject to extensive and ongoing regulatory requirements for manufacturing, labeling, packaging, distribution, adverse event reporting, storage, advertising, promotion, import, export, sampling and record-keeping. These requirements include submissions of safety and other post-marketing information and reports, registration, as well as continued compliance with cGMP regulations, good laboratory practices, or GLPs, and GCPs for any clinical trials that we conduct post-approval, all of which may result in significant expense and limit our ability to commercialize such products. In addition, any regulatory approvals that we receive for our product candidates may also be subject to limitations on the approved indicated uses for which the product may be marketed or to the conditions of approval, or contain requirements for potentially costly post-marketing testing, including Phase 4 clinical trials, and surveillance to monitor the safety and efficacy of the product candidate. The FDA may also require a REMS as a condition of approval of our product candidates, which could include requirements for a medication guide, physician communication plans or additional elements to ensure safe use, such as restricted distribution methods, patient

registries and other risk minimization tools. Such regulatory requirements may differ from country to country depending on where we have received regulatory approval.

The FDA's, NMPA's, EMA's or comparable regulatory authorities' policies may change and additional government regulations may be enacted that could prevent, limit or delay regulatory approval of our product candidates. We cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative action, either in the United States or abroad. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory compliance, we may lose any marketing approval that we may have obtained and we may not achieve or sustain profitability. Moreover, if there are changes in the application of legislation or regulatory policies, or if problems are discovered with a product or our manufacture of a product, or if we or one of our distributors, licensees or co-marketers fails to comply with regulatory requirements, the regulators could take various actions. These include:

- issuing warning or untitled letters or holds on clinical trials;
- mandating modifications to promotional materials or require us to provide corrective information to healthcare practitioners, or require other restrictions on the labeling or marketing of such products;
- seeking an injunction or imposing civil or criminal penalties or monetary fines;
- suspension or imposition of restrictions on operations, including product manufacturing or marketing or withdrawal of the product from the market;
- seizure or detention of products, refusal to permit the import or export of products or voluntary or mandatory product recalls;
- suspension, modification or revocation of our marketing approvals;
- suspension of any ongoing clinical trials;
- refusal to approve pending applications or supplements to applications submitted by us;
- imposition of a REMS, which may include distribution or use restrictions; or
- requiring us to conduct additional post-market clinical trials, change our product labeling or submit additional applications for marketing authorization.

Moreover, the FDA and other regulatory authorities strictly regulate the promotional claims that may be made about biological products. In particular, a product may not be promoted for uses that are not approved by the FDA as reflected in the product's approved labeling. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of such off-label uses, and a company that is found to have improperly promoted off-label uses may be subject to significant civil, criminal and administrative penalties. The federal government has levied large civil and criminal fines against companies for alleged improper promotion of off-label use and has enjoined several companies from engaging in off-label promotion. The FDA has also requested that companies enter into consent decrees, corporate integrity agreements or permanent injunctions under which specified promotional conduct must be changed or curtailed. If we cannot successfully manage the promotion of our product candidates, if approved, we could become subject to significant liability, which would materially adversely affect our business and financial condition.

Noncompliance by us or any future collaborator with regulatory requirements regarding safety monitoring or pharmacovigilance, and with requirements related to the development of products for the pediatric population, can also result in significant financial penalties. Similarly, failure to comply with regulatory requirements regarding the protection of personal information can also lead to significant penalties and sanctions.

Noncompliance with EU requirements regarding safety monitoring or pharmacovigilance, and with requirements related to the development of products for the pediatric population, also can result in significant financial penalties. Similarly, failure to comply with the EU's requirements regarding the protection of personal information can also lead to significant penalties and sanctions.

Any government investigation of alleged violations of law could require us to expend significant time and resources in response and could generate negative publicity. The occurrence of any event or penalty described above may inhibit our ability to commercialize our product candidates and harm our business, financial condition, results of operations and prospects.

If any of these events occurs, our ability to sell such product may be impaired, and we may incur substantial additional expense to comply with regulatory requirements, which could harm our business, financial condition, results of operations and prospects.

Obtaining and maintaining regulatory approval of our product candidates in one jurisdiction does not mean that we will be successful in obtaining regulatory approval of our product candidates in other jurisdictions.

Obtaining and maintaining regulatory approval of our product candidates in one jurisdiction does not guarantee that we will be able to obtain or maintain regulatory approval in any other jurisdiction, while a failure or delay in obtaining regulatory approval in one jurisdiction may have a negative effect on the regulatory approval process in others. For example, even if the FDA grants marketing approval of a product candidate, comparable foreign regulatory authorities must also approve the manufacturing, marketing and promotion of the product candidate in those countries. Approval and licensure procedures vary among jurisdictions and can involve requirements and administrative review periods different from, and greater than, those in the United States, including additional preclinical studies or clinical trials as clinical trials conducted in one jurisdiction may not be accepted by regulatory authorities in other jurisdictions. In many jurisdictions outside the United States, a product candidate must be approved for reimbursement before it can be approved for sale in that jurisdiction. In some cases, the price that we intend to charge for our products is also subject to approval.

We may also submit marketing applications in other countries. Regulatory authorities in jurisdictions outside of the United States have requirements for approval of product candidates with which we must comply prior to marketing in those jurisdictions. Obtaining comparable foreign regulatory approvals and compliance with comparable foreign regulatory requirements could result in significant delays, difficulties and costs for us and could delay or prevent the introduction of our products in certain countries. If we fail to comply with the regulatory requirements in international markets and/or receive applicable marketing approvals, our target market will be reduced and our ability to realize the full market potential of our product candidates will be harmed.

Disruptions at the FDA and other government agencies caused by funding shortages or global health concerns could hinder their ability to hire, retain or deploy key leadership and other personnel, or otherwise prevent new or modified products from being developed, or approved or commercialized in a timely manner or at all, which could negatively impact our business.

The ability of the FDA to review and approve new products can be affected by a variety of factors, including government budget and funding levels, statutory, regulatory, and policy changes, the FDA's ability to hire and retain key personnel and accept the payment of user fees, and other events that may otherwise affect the FDA's ability to perform routine functions. Average review times at the agency have fluctuated in recent years as a result. In addition, government funding of other government agencies that fund research and development activities is subject to the political process, which is inherently fluid and unpredictable. Disruptions at the FDA and other agencies may also slow the time necessary for new biologics to be reviewed and/or approved by necessary government agencies, which would adversely affect our business. For example, over the last several years, including for 35 days beginning on December 22, 2018, the U.S. government has shut down several times and certain regulatory agencies, such as the FDA, have had to furlough critical FDA employees and stop critical activities. If a prolonged government shutdown occurs, or if global health concerns continue to prevent the FDA or other regulatory authorities from conducting their regular inspections, reviews, or other regulatory activities, it could significantly impact the ability of the FDA or other regulatory authorities to timely review and process our regulatory submissions, which could have a material adverse effect on our business.

We may expend our limited resources to pursue a particular product candidate or indication and fail to capitalize on product candidates or indications that may be more profitable or for which there is a greater likelihood of success.

Due to several factors, we may again change our development plans. Because we have limited financial and managerial resources, we must prioritize our research programs and will need to focus our discovery and development on select product candidates and indications. Correctly prioritizing our research and development activities is particularly important for us due to the breadth of potential product candidates and indications that we believe could be pursued using our platform technologies. Specifically, we believe our SAA technology's broad applicability allows us to develop a wide array of product candidate modalities, such as ADCs, bispecific antibodies, PEGylated peptides, modified cytokines and immuno-stimulating antibody complexes. While we expect to add new franchises as we expand our technology platform and explore new disease areas, we may not have the resources necessary to pursue all of the potential applications of our technology. As a result, we may forego or delay pursuit of opportunities with potential product candidates or for certain indications that later prove to have greater prospects for success or return on our investment. Our resource allocation decisions may cause us to fail to capitalize on viable commercial products or profitable market opportunities. Our spending on current and future research and development programs and product candidates for specific indications may not yield any commercially viable products. If we do not accurately evaluate the commercial potential or target market for a particular product candidate, we may also relinquish valuable rights to that product candidate through collaboration, licensing or other royalty arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to such product candidate.

We may not be successful in our efforts to identify or discover additional product candidates in the future.

Our research programs may initially show promise in identifying potential product candidates, yet fail to yield product candidates for clinical development for a number of reasons, including:

- our inability to design such product candidates with the properties that we desire; or
- potential product candidates may, on further study, be shown to have harmful side effects or other characteristics that indicate that they are unlikely to be products that will receive marketing approval and achieve market acceptance.

Research programs to identify new product candidates require substantial technical, financial and human resources. If we are unable to identify suitable additional candidates for preclinical and clinical development, our opportunities to successfully develop and commercialize therapeutic products will be limited.

Risks Related to Manufacturing and Reliance on Third Parties

We rely on third parties to conduct, supervise and monitor our clinical trials and perform some of our research and preclinical studies. If these third parties do not satisfactorily carry out their contractual duties or fail to meet expected deadlines, our development programs may be delayed or subject to increased costs, each of which may have an adverse effect on our business and prospects.

We do not have the ability to conduct all aspects of our preclinical testing or clinical trials ourselves. As a result, we are, and expect to remain, dependent on third parties to conduct our preclinical studies and clinical trials, including our ongoing Phase 1 clinical trials and any future clinical trials of our product candidates. Specifically, CROs that manage preclinical studies and our clinical trials as well as clinical investigators and consultants play a significant role in the conduct of our preclinical studies and clinical trials and the subsequent collection and analysis of data. The timing of the initiation and completion of these studies and trials will therefore be partially controlled by such third parties and may result in delays to our development programs. Nevertheless, we are responsible for ensuring that each of our preclinical studies and clinical trials is conducted in accordance with the applicable protocol, legal requirements, and scientific standards, and our reliance on the CROs and other third parties does not relieve us of our regulatory responsibilities. We and these third parties are required to comply with GLP and GCP requirements, which are regulations and guidelines enforced by the FDA, the Competent Authorities of the Member States of the European Economic Area, and comparable foreign regulatory authorities for all of our product candidates in clinical development. Regulatory authorities enforce these GLP and GCP requirements through

periodic inspections of preclinical study sites, trial sponsors, clinical trial investigators and clinical trial sites. If we or any of these third parties or clinical trial sites fail to comply with applicable GLP or GCP requirements, the data generated in our preclinical studies and clinical trials may be deemed unreliable, and the FDA, NMPA, EMA or comparable regulatory authorities may require us to perform additional preclinical or clinical trials before approving our marketing applications. Upon inspection, such regulatory authorities may not determine that any of our clinical trials comply with the GCP regulations. In addition, our clinical trials must be conducted with product produced under cGMP regulations and will require a large number of test patients. Our failure or any failure by these third parties to comply with these regulations or to recruit a sufficient number of patients may require us to stop and/or repeat clinical trials, which would delay the marketing approval process. Moreover, our business may be implicated if any of these third parties violates federal or state fraud and abuse or false claims laws and regulations or healthcare privacy and security laws.

Any such CROs, clinical trial investigators or other third parties on which we rely are not and will not be our employees and, except for remedies available to us under our agreements with such third parties, we cannot control whether or not they devote adequate time and resources to our development activities or perform as contractually required. If any of these third parties fails to meet expected deadlines, adhere to our clinical protocols or meet regulatory requirements, otherwise performs in a substandard manner, or terminates its engagement with us, the timelines for our development programs may be delayed or our development activities may be suspended or terminated. If any of our clinical trial sites terminates for any reason, we may experience the loss of follow-up information on subjects enrolled in such clinical trials unless we are able to transfer those subjects to another qualified clinical trial site, which may be difficult or impossible. In addition, clinical trial investigators for our clinical trials may serve as scientific advisors or consultants to us from time to time and may receive cash or equity compensation in connection with such services. If these relationships and any related compensation result in perceived or actual conflicts of interest, or the FDA, NMPA, EMA or any comparable regulatory authority concludes that the financial relationship may have affected the interpretation of the trial, the integrity of the data generated at the applicable clinical trial site may be questioned and the utility of the clinical trial itself may be jeopardized, which could result in the delay or rejection of any marketing application we submit by the FDA, NMPA, EMA or any comparable regulatory authority. Any such delay or rejection could prevent us from commercializing our product candidates.

Furthermore, these third parties may also have relationships with other entities, some of which may be our competitors. If these third parties do not successfully carry out their contractual duties, meet expected deadlines or conduct our clinical trials in accordance with regulatory requirements or our stated protocols, we will not be able to obtain, or may be delayed in obtaining, marketing approvals for our product candidates and will not be able to, or may be delayed in our efforts to, successfully commercialize our products.

Switching or adding third parties to conduct our preclinical studies and clinical trials involves substantial cost and requires extensive management time and focus. In addition, there is a natural transition period when a new third party commences work. As a result, delays occur, which can materially impact our ability to meet our desired clinical development timelines.

We rely on third parties for the manufacturing and supply of certain of our product candidates for use in preclinical testing and clinical trials, which supply may become limited or interrupted or may not be of satisfactory quality and quantity.

We do not have any manufacturing facilities. We produce relatively small quantities of product for evaluation in our research programs in our laboratory. We rely on third parties for the manufacture of a portion of our product candidates for preclinical testing and all of our product candidates for clinical testing and we will continue to rely on such third parties for commercial manufacture if any of our product candidates are approved. This reliance increases the risk that we will not have sufficient quantities of our product candidates or products, if approved, or such quantities at an acceptable cost or quality, which could delay, prevent or impair our development or commercialization efforts. Currently, our drug raw materials for our manufacturing activities are supplied by multiple source suppliers. We have agreements for the supply of drug materials with manufacturers or suppliers that we believe have sufficient capacity to meet our demands. In addition, we believe that adequate alternative sources for such supplies exist. However, there is a risk that, if supplies are interrupted, it would materially harm our business.

Furthermore, all entities involved in the preparation of therapeutics for clinical trials or commercial sale, including our existing contract manufacturers for our product candidates, are subject to extensive regulation. Components of a finished therapeutic product approved for commercial sale or used in clinical trials must be manufactured in accordance with cGMP requirements. These regulations govern manufacturing processes and procedures, including record keeping, and the implementation and operation of quality systems to control and assure the quality of investigational products and products approved for sale. Poor control of production processes can lead to the introduction of contaminants, or to inadvertent changes in the properties or stability of our product candidates that may not be detectable in final product testing. We or our contract manufacturers must supply all necessary documentation in support of a BLA on a timely basis and must adhere to the FDA's GLP and cGMP regulations enforced by the FDA through its facilities inspection program. Comparable foreign regulatory authorities may require compliance with similar requirements. We have analytical and process development capabilities and can manufacture non-cGMP material in our laboratory. We generally perform cell line, analytical and process development for our product candidates internally and manufacture the drug necessary to conduct non-GLP preclinical studies of our investigational product candidates. We occasionally outsource the production of research and development material. We do not have, and we do not currently plan to, acquire or develop the facilities or capabilities to manufacture bulk drug substance or filled drug product for use in human clinical trials. We rely on third-party manufacturers to produce the bulk drug substances required for our clinical trials and expect to continue to rely on third parties to manufacture and test clinical trial drug supplies for the foreseeable future. The facilities and quality systems of our third-party contract manufacturers must pass a pre-approval inspection for compliance with the applicable regulations as a condition of marketing approval of our product candidates. We do not control the manufacturing activities of, and are completely dependent on, our contract manufacturers for compliance with cGMP regulations.

In the event that any of our manufacturers fails to comply with such requirements or to perform its obligations to us in relation to quality, timing or otherwise, or if our supply of components or other materials becomes limited or interrupted for other reasons, including due to the impact of the COVID-19 pandemic or the ongoing conflict between Ukraine and Russia, we may be forced to manufacture the materials ourselves, for which we currently do not have the capabilities or resources, or enter into an agreement with another third-party, which we may not be able to do on commercially reasonable terms, if at all. In particular, any replacement of our manufacturers could require significant effort and expertise because there may be a limited number of qualified replacements. In some cases, the technical skills or technology required to manufacture our product candidates may be unique or proprietary to the original manufacturer and we may have difficulty transferring such skills or technology to another third-party and a feasible alternative may not exist. In addition, certain of our product candidates and our own proprietary methods have never been produced or implemented outside of our company, and we may therefore experience delays to our development programs when we attempt to establish new third-party manufacturing arrangements for these product candidates or methods. These factors would increase our reliance on such manufacturer or require us to obtain a license from such manufacturer in order to have another third-party manufacture our product candidates. If we are required to or voluntarily change manufacturers for any reason, we will be required to verify that the new manufacturer maintains facilities and procedures that comply with quality standards and with all applicable regulations and guidelines. We will also need to verify, such as through a manufacturing comparability study, that any product produced by the new manufacturer is equivalent to that produced in a prior facility. The delays associated with the verification of a new manufacturer and equivalent product could negatively affect our ability to develop product candidates in a timely manner or within budget.

A third-party's failure to execute on our manufacturing requirements, do so on commercially reasonable terms and timelines and comply with cGMP requirements could adversely affect our business in a number of ways, including:

- inability to meet our product specifications and quality requirements consistently;
- an inability to initiate or continue clinical trials of our product candidates under development;
- delay in submitting regulatory applications, or receiving marketing approvals, for our product candidates, if at all;
- loss of the cooperation of future collaborators;

- subjecting third-party manufacturing facilities or our manufacturing facilities to additional inspections by regulatory authorities;
- requirements to cease development or to recall batches of our product candidates; and
- in the event of approval to market and commercialize our product candidates, an inability to meet commercial demands for our product or any other future product candidates.

Manufacturing ADC products is complex and our third-party manufacturers may encounter difficulties in production. If any of our third-party manufacturers encounter such difficulties, our ability to provide supply of our product candidates for clinical trials or our products for patients, if approved, will likely be delayed or prevented.

Manufacturing ADC products is complex and requires the use of innovative technologies to handle living cells. Each lot of an approved biological product must undergo thorough testing for identity, strength, quality, purity and potency. Manufacturing these products requires facilities specifically designed for and validated for this purpose and sophisticated quality assurance and quality control procedures are necessary. Slight deviations anywhere in the manufacturing process, including filling, labeling, packaging, storage and shipping and quality control and testing, may result in lot failures, product recalls or spoilage. When changes are made to the manufacturing process, we may be required to provide preclinical and clinical data showing the comparable identity, strength, quality, purity or potency of the products before and after such changes. If microbial, viral or other contaminations are discovered at manufacturing facilities, such facilities may need to be closed for an extended period of time to investigate and remedy the contamination, which will likely delay clinical trials and adversely harm our business. The use of biologically derived ingredients can also lead to allegations of harm, including infections or allergic reactions, or closure of product facilities due to possible contamination.

In addition, there are risks associated with large scale manufacturing for clinical trials or commercial scale including, among others, cost overruns, potential problems with process scale-up, process reproducibility, stability issues, compliance with good manufacturing practices, lot consistency, significant lead times and timely availability of raw materials. Even if we obtain marketing approval for any of our product candidates, we or our manufacturers may not be able to manufacture the approved product to specifications acceptable to the FDA, NMPA, EMA or comparable foreign regulatory authorities, to produce it in sufficient quantities to meet the requirements for the potential commercial launch of the product or to meet potential future demand. If our manufacturers are unable to produce sufficient quantities for clinical trials or for commercialization, our development and commercialization efforts would be impaired, which would have an adverse effect on our business, financial condition, results of operations and growth prospects.

Due to the early nature of our product candidates, the drug product may not be stable over time, causing changes to be made to the manufacturing or storage process which will likely result in delays or stopping the development of the product candidate.

Changes in methods of product candidate manufacturing may result in additional costs or delays.

As product candidates progress through preclinical to late-stage clinical trials to marketing approval and commercialization, it is common that various aspects of the development program, such as manufacturing methods, are altered along the way in an effort to optimize yield, manufacturing batch size, change drug product dosage form, minimize costs and achieve consistent quality and results. While we have successfully scaled bacterial fermentation of our ReCODE platform to the commercial-scale of 50,000 liters and have scaled our EuCODE platform to 2,000 liters and we have manufactured our product candidates with a new dosage lyophilized formulation and demonstrated analytical comparability with pre-change clinical trial materials, further changes may be required to the manufacturing processes and deviations anywhere in the manufacturing process, including filling, labeling, packaging, storage and shipping and quality control and testing, may result in lot failures, product recalls or spoilage. We may also use different formulations in the same clinical trial. When changes are made to the manufacturing process, we may be required to provide preclinical and clinical data showing the comparable identity, strength, quality, purity or potency of the products before and after such changes. Any of these changes could also cause our product candidates to perform differently and affect the safety and efficacy results of current and planned clinical trials or other future clinical trials conducted with the altered materials. This could delay completion of clinical trials, require the conduct of bridging clinical trials or the repetition of one or more clinical trials, increase clinical trial costs, delay approval of our product candidates and jeopardize our ability to commercialize our product candidates and generate revenue.

Our reliance on third parties requires us to share our trade secrets, which increases the possibility that a competitor will discover them or that our trade secrets will be misappropriated or disclosed.

Because we rely on third parties to research and develop and to manufacture our product candidates, we must share trade secrets with them. We seek to protect our proprietary technology in part by entering into confidentiality agreements and, if applicable, material transfer agreements, consulting agreements or other similar agreements with our advisors, employees, third-party contractors and consultants prior to beginning research or disclosing proprietary information. These agreements typically limit the rights of the third parties to use or disclose our confidential information, including our trade secrets. Despite the contractual provisions employed when working with third parties, the need to share trade secrets and other confidential information increases the risk that such trade secrets become known by our competitors, are inadvertently incorporated into the technology of others, or are disclosed or used in violation of these agreements. Given that our proprietary position is based, in part, on our know-how and trade secrets, a competitor's independent discovery of our trade secrets or other unauthorized use or disclosure would impair our competitive position and may have a material adverse effect on our business.

In addition, these agreements typically restrict the ability of our advisors, employees, third-party contractors and consultants to publish data potentially relating to our trade secrets, although our agreements may contain certain limited publication rights. For example, any academic institution that we may collaborate with will likely expect to be granted rights to publish data arising out of such collaboration and any joint research and development programs may require us to share trade secrets under the terms of our research and development or similar agreements. Despite our efforts to protect our trade secrets, our competitors may discover our trade secrets, either through breach of our agreements with third parties, independent development or publication of information by any of our third-party collaborators. A competitor's discovery of our trade secrets would impair our competitive position and have an adverse impact on our business.

Risks Related to Commercialization

Any approved products may fail to achieve the degree of market acceptance by physicians, patients, hospitals, cancer treatment centers, healthcare payors and others in the medical community necessary for commercial success.

If any of our product candidates receive marketing approval, they may nonetheless fail to gain sufficient market acceptance by physicians, patients, healthcare payors and others in the medical community. For example, current cancer treatments like chemotherapy and radiation therapy are well established in the medical community, and physicians may continue to rely on these treatments. Most of our product candidates target mechanisms for which there are limited or no currently approved products, which may result in slower adoption by physicians, patients and payors. If our product candidates do not achieve an adequate level of acceptance, we may not generate significant product revenue and we may not become profitable. The degree of market acceptance of our product candidates, if approved for commercial sale, will depend on a number of factors, including:

- efficacy and potential advantages compared to alternative treatments;
- our ability to offer our products for sale at competitive prices;
- convenience and ease of administration compared to alternative treatments;
- the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies;
- the availability of coverage and adequate reimbursement from government and commercial third-party payors, and the willingness of patients to pay out of pocket for our products, once approved, in the absence of adequate third party payor reimbursement;
- the strength of marketing and distribution support; and
- the prevalence and severity of any side effects.

We may not be able to successfully commercialize our product candidates, if approved, due to unfavorable pricing regulations or third-party coverage and reimbursement policies, which could make it difficult for us to sell our product candidates profitably.

Obtaining coverage and reimbursement approval for a product from a government or other third-party payor is a time-consuming and costly process, with uncertain results, that could require us to provide supporting scientific, clinical and cost effectiveness data for the use of our products to the payor. There may be significant delays in obtaining such coverage and reimbursement for newly approved products, and coverage may not be available, or may be more limited than the purposes for which the product is approved by the FDA, NMPA, EMA or comparable foreign regulatory authorities. Moreover, eligibility for coverage and reimbursement does not imply that a product will be paid for in all cases or at a rate that covers our costs, including research, development, intellectual property, manufacture, sale and distribution expenses. Interim reimbursement levels for new products, if applicable, may also not be sufficient to cover our costs and may not be made permanent. Reimbursement rates may vary according to the use of the product and the clinical setting in which it is used, may be based on reimbursement levels already set for lower cost products and may be incorporated into existing payments for other services. Net prices for products may be reduced by mandatory discounts or rebates required by government healthcare programs or private payors, by any future laws limiting drug prices and by any future relaxation of laws that presently restrict imports of product from countries where they may be sold at lower prices than in the United States.

There is significant uncertainty related to the insurance coverage and reimbursement of newly approved products. In the United States, there is no uniform policy among third-party payors for coverage and reimbursement. Third-party payors often rely upon Medicare coverage policy and payment limitations in setting reimbursement policies, but also have their own methods and approval process apart from Medicare coverage and reimbursement determinations. Therefore, one third-party payor's determination to provide coverage for a product does not assure that other payors will also provide coverage for the product.

Coverage and reimbursement by a third-party payor may depend upon a number of factors, including the third-party payor's determination that use of a product is:

- a covered benefit under its health plan;
- safe, effective and medically necessary;
- appropriate for the specific patient;
- cost-effective; and
- neither experimental nor investigational.

Reimbursements may not be available for all products that we commercialize and, if coverage and reimbursement is available, we cannot be sure what level of reimbursement will be available. Obtaining reimbursement for our products may be particularly difficult because of the higher prices often associated with branded therapeutics and therapeutics administered under the supervision of a physician. Our inability to promptly obtain coverage and adequate reimbursement rates from both government-funded and private payors for any approved products that we develop could have a material adverse effect on our operating results, our ability to raise capital needed to commercialize products and our overall financial condition.

Reimbursement may impact the demand for, and the price of, any product for which we obtain marketing approval. Even if we obtain coverage for a given product by a third-party payor, the resulting reimbursement payment rates may not be adequate or may require co-payments that patients find unacceptably high. Patients who are prescribed medications for the treatment of their conditions, and their prescribing physicians, generally rely on third-party payors to reimburse all or part of the costs associated with those medications. Patients are unlikely to use our products unless coverage is provided and reimbursement is adequate to cover all or a significant portion of the cost of our products. Therefore, coverage and adequate reimbursement are critical to a new product's acceptance. Coverage decisions may depend upon clinical and economic standards that disfavor new products when more established or lower cost therapeutic alternatives are already available or subsequently become available.

For products administered under the supervision of a physician, obtaining coverage and adequate reimbursement may be particularly difficult because of the higher prices often associated with such drugs. Additionally, separate reimbursement for the product itself may or may not be available. Instead, the hospital or administering physician may be reimbursed only for providing the treatment or procedure in which our product is used. Further, from time to time, the Centers for Medicare & Medicaid Services, or CMS, revises the reimbursement systems used to reimburse healthcare providers, including the Medicare Physician Fee Schedule and Hospital Outpatient Prospective Payment System, which may result in reduced Medicare payments.

We expect to experience pricing pressures in connection with the sale of any of our product candidates due to the trend toward managed healthcare, the increasing influence of health maintenance organizations, and additional legislative changes. The downward pressure on healthcare costs in general, particularly prescription medicines, medical devices and surgical procedures and other treatments, has become very intense. As a result, increasingly high barriers are being erected to the successful commercialization of new products. Further, the adoption and implementation of any future governmental cost containment or other health reform initiative may result in additional downward pressure on the price that we may receive for any approved product. In addition, coverage policies and third-party payor reimbursement rates may change at any time. Therefore, even if favorable coverage and reimbursement status is attained for one or more products for which we receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

Additionally, while we currently intend to rely on commercially-available diagnostic tests, we may in the future be required to develop, alone or through a diagnostic test collaborator, new companion diagnostic tests for use with our product candidates. In this case we, or our collaborators, would be required to obtain coverage and reimbursement for these tests separate and apart from the coverage and reimbursement we may seek for our product candidates. For any newly-developed companion diagnostic test, there would be significant uncertainty regarding our ability to obtain coverage and adequate reimbursement for the same reasons applicable to our product candidates. Outside of the United States, many countries require approval of the sale price of a product before it can be marketed, and the pricing review period only begins after marketing or product licensing approval is granted.

To obtain reimbursement or pricing approval in some of these countries, we may be required to conduct a clinical trial that compares the cost-effectiveness of our product candidate to other available therapies. In some foreign markets, prescription pharmaceutical pricing remains subject to continuing governmental control even after initial approval is granted. As a result, we might obtain marketing approval for a product candidate in a particular country, but then be subject to price regulations that delay our commercial launch of the product, possibly for lengthy time periods, and negatively impact the revenue, if any, we are able to generate from the sale of the product in that country. Adverse pricing limitations may hinder our ability to recoup our investment in one or more product candidates, even if such product candidates obtain marketing approval.

The market opportunities for any current or future product candidate we develop, if approved, may be limited to those patients who are ineligible for established therapies or for whom prior therapies have failed, and may be small.

Cancer therapies are sometimes characterized by line of therapy (first-line, second-line, third-line, etc.) and the FDA often approves new therapies initially only for a particular line or lines of use. When cancer is detected early enough, first-line therapy, usually chemotherapy, hormone therapy, surgery, radiation therapy or a combination of these, is sometimes adequate to cure the cancer or prolong life without a cure. Second- and third-line therapies are administered to patients when prior therapy is not effective. We expect to initially seek approval of ARX517 and any other product candidates we develop as a therapy for patients who have received one or more prior treatments. Subsequently, for those products that prove to be sufficiently beneficial, if any, we would expect to seek approval potentially as a first-line therapy, but product candidates we develop, even if approved, may not be approved for first-line therapy, and, prior to any such approvals, we may have to conduct additional clinical trials.

The number of patients who have the cancers we are targeting as well as the subset of patients with these cancers in a position to receive a particular line of therapy may turn out to be lower than expected. Additionally, the potentially addressable patient population for our current programs or future product candidates may be limited, if approved. Further, new therapies may change the estimated incidence or prevalence of the cancers that we are targeting. Even if we obtain significant market share for any product candidate, if approved, if the potential target populations are small, we may never achieve profitability without obtaining marketing approval for additional indications, including to be used as first- or second-line therapy.

Our product candidates for which we intend to seek approval as biological products may face competition sooner than anticipated.

The Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, or the Affordable Care Act or ACA, signed into law on March 23, 2010, includes a subtitle called the Biologics Price Competition and Innovation Act of 2009, or BPCIA, which created an abbreviated approval pathway for biological products that are biosimilar to or interchangeable with FDA-licensed reference biological product. Under the BPCIA, an application for a biosimilar product may not be submitted to the FDA until four years following the date that the reference product was first licensed by the FDA. In addition, the approval of a biosimilar product may not be made effective by the FDA until 12 years from the date on which the reference product was first licensed. During this 12-year period of exclusivity, another company may still market a competing version of the reference product if the FDA approves a full BLA for the competing product containing the sponsor's own preclinical data and data from adequate and well-controlled clinical trials to demonstrate the safety, purity and potency of their product.

We believe that any of our product candidates approved as a biological product under a BLA should qualify for the 12-year period of exclusivity. However, the FDA may determine that previously marketed biologics may limit or eliminate the 12-year exclusivity. There is also a risk that this exclusivity could be shortened due to congressional action, court decisions or otherwise, or that the FDA will not consider our product candidates to be reference products for competing products, potentially creating the opportunity for generic competition sooner than anticipated. Other aspects of the BPCIA, some of which may impact the BPCIA exclusivity provisions, have also been the subject of recent litigation. Moreover, the extent to which a biosimilar, once approved, will be substituted for any one of our reference products in a way that is similar to traditional generic substitution for non-biological products is not yet clear, and will depend on a number of marketplace and regulatory factors that are still developing.

If any approved products are subject to biosimilar competition sooner than we expect, we will face significant pricing pressure and our commercial opportunity will be limited.

If the market opportunities for any of our product candidates are smaller than we believe they are, our revenue may be adversely affected, and our business may suffer.

We are focused initially on the development of treatments for cancer. Our projections of addressable patient populations that have the potential to benefit from treatment with our product candidates are based on estimates. If any of our estimates are inaccurate, the market opportunities for any of our product candidates could be significantly diminished and have an adverse material impact on our business.

If any of our product candidates are approved for marketing and commercialization and we are unable to establish sales and marketing capabilities or enter into agreements with third parties to sell and market our product candidates, we will be unable to successfully commercialize our product candidates if they are approved.

We have no sales, marketing or distribution capabilities or experience. To achieve commercial success for any approved product for which we retain sales and marketing responsibilities, we must either develop a sales and marketing organization, which would be expensive and time consuming, or outsource these functions to other third parties. In the future, we may choose to build a focused sales and marketing infrastructure to sell, or participate in sales activities with our collaborators for, some of our product candidates if they are approved.

There are risks involved with both establishing our own sales and marketing capabilities and entering into arrangements with third parties to perform these services. For example, recruiting and training a sales force is expensive and time consuming and could delay any product launch. If the commercial launch of a product candidate for which we recruit a sales force and establish marketing capabilities is delayed or does not occur for any reason, we would have prematurely or unnecessarily incurred these commercialization expenses. This may be costly, and our investment would be lost if we cannot retain or reposition our sales and marketing personnel.

Factors that may inhibit our efforts to commercialize future products on our own include:

- our inability to recruit and retain adequate numbers of effective sales and marketing personnel;
- the inability of sales personnel to obtain access to physicians or educate adequate numbers of physicians on the benefits of prescribing any future products;
- the lack of complementary products to be offered by sales personnel, which may put us at a competitive disadvantage relative to companies with more extensive product portfolios; and
- unforeseen costs and expenses associated with creating an independent sales and marketing organization.

If we enter into arrangements with third parties to perform sales, marketing and distribution services, our product revenue or the profitability of these product revenue to us are likely to be lower than if we were to market and sell any products that we develop ourselves. In addition, we may not be successful in entering into arrangements with third parties to sell and market our product candidates or may be unable to do so on terms that are favorable to us. In entering into third-party marketing or distribution arrangements, any revenue we receive will depend upon the efforts of the third parties, which may not establish adequate sales and distribution capabilities or devote the necessary resources and attention to sell and market any future products effectively. If we do not establish sales and marketing capabilities successfully, either on our own or in collaboration with third parties, we may not be successful in commercializing our product candidates.

Any product candidate for which we obtain marketing approval could be subject to post-marketing restrictions or recall or withdrawal from the market, and we may be subject to penalties if we fail to comply with regulatory requirements or if we experience unanticipated problems with our product candidates, when and if any of them are approved.

The FDA and other federal and state agencies, including the U.S. Department of Justice, or DOJ, closely regulate compliance with all requirements governing prescription drug products, including requirements pertaining to marketing and promotion of products in accordance with the provisions of the approved labeling and manufacturing of products in accordance with cGMP requirements. The FDA and DOJ impose stringent restrictions on manufacturers' communications regarding off-label use and if we do not market our products for their approved indications, or if other of our marketing claims are deemed false or misleading, we may be subject to enforcement action. Violations of such requirements may lead to investigations alleging violations of the Food, Drug and Cosmetic Act and other statutes, including the False Claims Act and other federal and state healthcare fraud and abuse laws as well as state consumer protection laws.

Our failure to comply with all regulatory requirements, and later discovery of previously unknown adverse events or other problems with our products, manufacturers or manufacturing processes, may yield various results, including:

- litigation involving patients taking our products;
- restrictions on such products, manufacturers or manufacturing processes;
- restrictions on the labeling or marketing of a product;
- restrictions on product distribution or use;
- requirements to conduct post-marketing studies or clinical trials;
- warning or untitled letters;
- withdrawal of the products from the market;
- refusal to approve pending applications or supplements to approved applications that we submit;
- recall of products;
- fines, restitution or disgorgement of profits or revenue;
- suspension or withdrawal of marketing approvals;
- suspension of any ongoing clinical trials;
- damage to relationships with any potential collaborators;
- unfavorable press coverage and damage to our reputation;
- refusal to permit the import or export of our products;
- product seizure; or
- injunctions or the imposition of civil or criminal penalties.

If any of these events occurs, our ability to sell such product may be impaired, and we may incur substantial additional expense to comply with regulatory requirements, which could adversely affect our business, financial condition and results of operations.

We face substantial competition, which may result in others discovering, developing or commercializing products more quickly or marketing them more successfully than us.

The development and commercialization of new products is highly competitive. We largely compete in the segments of the pharmaceutical, biotechnology and other related markets that develop cancer treatments. Our commercial opportunity could be reduced or eliminated if our competitors develop and commercialize products that are safer, more effective, have fewer or less severe side effects, are more convenient, or are less expensive than any products that we may develop. Our competitors also may obtain FDA or other regulatory approval for their products more rapidly than we may obtain approval for ours, if ever, which could result in our competitors establishing a strong market position before we are able to enter the market or make our development more complicated. Moreover, with the proliferation of new drugs and therapies into oncology, we expect to face increasingly intense competition as new technologies become available. If we fail to stay at the forefront of technological change, we may be unable to compete effectively. Any product candidates that we successfully develop and commercialize will compete with existing therapies and new therapies that may become available in the future. The highly competitive nature of and rapid technological changes in the biotechnology and pharmaceutical industries could render our product candidates or our technology obsolete, less competitive or uneconomical.

Other ADCs have already been approved and other products in the same class are further along in development. As more product candidates within a particular class of biological products proceed through clinical development to regulatory review and approval, the amount and type of clinical data that may be required by regulatory authorities may increase or change. Consequently, the results of our clinical trials for product candidates in those classes will likely need to show a risk benefit profile that is competitive with or more favorable than those products and product candidates in order to obtain marketing approval or, if approved, a product label that is favorable for commercialization. If the risk benefit profile is not competitive with those products or product candidates, we may have developed a product that is not commercially viable, that we are not able to sell profitably or that is unable to achieve favorable pricing or reimbursement. In such circumstances, our future product revenue and financial condition would be materially and adversely affected.

There are many companies pursuing a variety of approaches to protein conjugations and modifications. Multiple companies, including larger and more established companies, are pursuing traditional approaches that rely upon natural amino acids, usually a cysteine or lysine, as a conjugation site. Another approach looks to modify the sugar residues of naturally occurring amino acids. Our approach is to encode a non-natural amino acid at optimized positions within the proteins, and Sutro Biopharma, Synthorx Inc. and other early-stage companies also use this approach. Other companies using antibody-drug conjugates to target innate immune receptors include, but are not limited to, Actym Therapeutics, Mersana Therapeutics, and Takeda Pharmaceuticals. Immunotherapy and validated pathway approaches are further being pursued by many smaller biotechnology companies as well as larger pharmaceutical companies. We also face competition from validated pathway therapy treatments offered by companies such as AstraZeneca, Byondis, Daiichi Sankyo, Genentech, MacroGenics, Pieris Pharmaceuticals, Puma, Seattle Genetics, Spectrum Pharmaceuticals, and Zymeworks. We also face competition from companies that continue to invest in innovation in the antibody-drug conjugate field, including but not limited to AbbVie, ADC Therapeutics, Astellas Pharma, BioAtla, Celldex Therapeutics, CytomX Therapeutics, Eli Lilly and Company, GlaxoSmithKline, Genmab, ImmunoGen, Immunomedics, Millennium Pharmaceuticals, MorphoSys AG, Novartis, Pfizer, Sanofi, Seattle Genetics, Sutro Biopharma and VelosBio.

Many of our competitors, either alone or with their collaboration partners, have significantly greater financial resources and expertise in research and development, preclinical testing, clinical trials, manufacturing and marketing than we do. Future collaborations and mergers and acquisitions may result in further resource concentration among a smaller number of competitors. Smaller or early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These competitors will also compete with us in recruiting and retaining qualified scientific and management personnel and establishing clinical trial sites and subject registration for clinical trials, as well as in acquiring technologies complementary to, or that may be necessary for, our programs.

The key competitive factors affecting the success of all of our programs are likely to be efficacy, safety, and convenience. If we are not successful in developing, commercializing and achieving higher levels of reimbursement than our competitors, we will not be able to compete against them and our business would be materially harmed.

Risks Related to Our In-Licenses and Other Strategic Agreements

We are currently party to several in-license agreements under which we acquired rights to use, develop, manufacture and/or commercialize certain of our platform technologies and resulting product candidates. If we breach our obligations under these agreements, we may be required to pay damages, lose our rights to these technologies or both, which would adversely affect our business and prospects.

We rely, in part, on license and other strategic agreements, which subject us to various obligations, including diligence obligations with respect to development and commercialization activities, payment obligations for achievement of certain milestones and royalties on product sales, negative covenants and other material obligations. For example, we have exclusively licensed certain patent rights from The Scripps Research Institute, or TSRI, related to various aspects of our technology platform. If we fail to comply with the obligations under our license agreements, or use the intellectual property licensed to us in an unauthorized manner, we may be required to pay damages and our licensors may have the right to terminate the license. If our license agreements are terminated, we may not be able to develop, manufacture, market or sell the products covered by our agreements and those being tested or approved in combination with such products. Such an occurrence could materially adversely affect the value of the product candidates being developed under any such agreement.

In addition, the agreements under which we license intellectual property or technology to or from third parties are complex, and certain provisions in such agreements may be susceptible to multiple interpretations. The resolution of any contract interpretation disagreement that may arise could narrow what we believe to be the scope of our rights to the relevant intellectual property or technology or increase what we believe to be our financial or other obligations under the relevant agreement, either of which could have a material adverse effect on our business, financial condition, results of operations and prospects. Moreover, if disputes over intellectual property that we have licensed prevent or impair our ability to maintain our current licensing arrangements on commercially acceptable terms, we may be unable to successfully develop and commercialize the affected product candidates.

Our business also would suffer if any current or future licensors fail to abide by the terms of the license, if the licensors fail to enforce licensed patents against infringing third parties, if the licensed patents or other rights are found to be invalid or unenforceable, or if we are unable to enter into necessary licenses on acceptable terms.

Moreover, our licensors may own or control intellectual property that has not been licensed to us and, as a result, we may be subject to claims, regardless of their merit, that we are infringing or otherwise violating the licensor's rights.

In addition, while we cannot currently determine the amount of the royalty obligations we would be required to pay on sales of future products, if any, the amounts may be significant. The amount of our future royalty obligations will depend on the technology and intellectual property we use in products that we successfully develop and commercialize, if any. Therefore, even if we successfully develop and commercialize products, we may be unable to achieve or maintain profitability.

If we are unable to successfully obtain rights to required third-party intellectual property rights or maintain the existing intellectual property rights we have, we may have to abandon development of the relevant research programs or product candidates and our business, financial condition, results of operations and prospects could suffer.

We are dependent on our license agreements and research and development agreements, or R&D Agreements, with various partners to develop and commercialize products using our technologies in various fields and indications as well as certain of our product candidates in certain geographies. The failure to maintain our R&D Agreements with our collaboration partners or the failure of our partners to perform their obligations under our R&D Agreements with them, could negatively impact our business.

We have granted various collaboration partners exclusive licenses to certain patents, information and know-how related to our technologies or product candidates, including rights to develop and commercialize ARX788 and ARX305 in China to NovoCodex. Consequently, our ability to realize value or generate any revenues from certain of our product candidates or in certain geographies for our product candidates depends on our collaboration partners' willingness and ability to develop and obtain regulatory approvals for and successfully commercialize our

out-licensed product candidates or other product candidates using our technology. We have limited control over the amount and timing of resources that our collaboration partners will dedicate to these efforts. In particular, we will not be entitled to receive additional milestone or royalty payments from our existing collaborations absent further development and eventual commercialization of the licensed product candidates or other product candidates using our technology.

We are subject to a number of other risks associated with our dependence on our license agreements and R&D Agreements, including:

- our collaboration partners may not comply with applicable regulatory requirements with respect to developing or commercializing products under our agreements with them, which could adversely impact development, regulatory approval and eventual commercialization of such products. For example, our collaboration partners' failure to comply with existing or future laws and regulations related to the management of human genetic resources (including materials and information) in China could lead to government enforcement actions, which could include fines, suspension of related activities and confiscation of related human genetic resources and gains generated from conducting these activities, or breach liability. Compliance or the failure to comply with such laws could increase the costs of, limit and cause significant delay in their clinical studies and research and development activities, which could materially and adversely affect our business and prospects as well;
- we and our collaboration partners could disagree as to future development plans and our partners may delay initiation of or cease research efforts, preclinical studies or clinical trials;
- there may be disputes between us and our collaboration partners, including disagreements regarding the terms of the applicable agreement or scope of the license, that may result in the delay of or failure to achieve development, regulatory and commercial objectives that would result in milestone or royalty payments to us, the delay or termination of any future development or commercialization of our product candidates or other product candidates using our technology, and/or costly litigation or arbitration that diverts our management's attention and resources;
- our collaboration partners may not provide us with timely and accurate information regarding development progress and activities under the applicable agreement, which could adversely impact our ability to report progress to our investors and otherwise plan our own development activities;
- business combinations or significant changes in our collaboration partners' business strategy may adversely affect their ability or willingness to perform their obligations under the applicable agreement; collaborators have significant discretion in determining the efforts and resources that they will apply to a collaboration;
- a collaborator with marketing and distribution rights to one or more products may not commit sufficient resources to their marketing and distribution;
- collaborations may be terminated and, if terminated, may result in a need for additional capital to pursue further development or commercialization of the applicable product candidates;
- our collaboration partners may not properly maintain or defend our licensed intellectual property rights or may use our proprietary information in such a way as to invite litigation that could jeopardize or invalidate our intellectual property rights or expose us to potential litigation;
- safety and efficacy data generated by our partners may adversely affect our product candidates or the market perception of our product candidates; and
- the royalties we are eligible to receive from our collaboration partners may be reduced or eliminated based upon their and our ability to maintain or defend our intellectual property rights.

With respect to ARX788 and ARX305, we have licensed development and commercialization rights in China to NovoCodex. We have limited control over NovoCodex's development, regulatory and commercialization activities with respect to these product candidates in China; however, NovoCodex's activities in China could have significant consequences to our ability to successfully develop, obtain regulatory approval for and commercialize ARX788 and ARX305 in the United States and other territories for which we maintain rights. For example, if NovoCodex experiences a clinical failure or safety issues or receives negative decisions from regulatory authorities in China, it could negatively impact the value and prospects of the product candidate in the territories in which we retain rights. Additionally, although we have not been required to repeat Phase 1 trials to initiate Phase 2 or Phase 3 HER2-positive metastatic breast cancer trials in the United States, the FDA or comparable foreign regulatory authorities may not interpret the results of the trials being conducted in China by our partner, NovoCodex as we do, and may require additional trials.

Our license agreements and R&D Agreements are subject to early termination, including through the collaboration partner's right to terminate without cause upon advance notice to us. For example, in June 2021, Agensys, a wholly owned subsidiary of Astellas Pharma, terminated a collaboration agreement with us. Agensys terminated the agreement due to a lack of efficacy demonstrated by ASP-1235, a product candidate discovered through our collaboration. If an agreement is terminated early, we may not be able to find another collaborator for the further development or commercialization of the licensed product candidate or technology in the applicable field or geography on acceptable terms, or at all, and we may otherwise be unable to pursue continued development on our own. To the extent we enter into additional agreements for the development and commercialization of our product candidates, we would likely be similarly dependent on the performance of those third parties and subject to similar risks.

We may not be successful in establishing and maintaining additional research and development agreements, which could adversely affect our ability to develop and commercialize our product candidates.

We intend to continue evaluating and, as deemed appropriate, enter into additional out-licensing and research and development agreements, including potentially with major biotechnology or pharmaceutical companies. We face significant competition in seeking appropriate partners for our product candidates, and the negotiation process is time-consuming and complex. In order for us to successfully partner our product candidates, potential partners must view these product candidates as having the requisite potential to demonstrate safety and efficacy and as being economically valuable in light of the terms that we are seeking and other available products for licensing by other companies. Due to our multiple existing license agreements and R&D Agreements, we may find it more difficult to secure additional collaborations for our technologies or product candidates if major biotechnology or pharmaceutical companies would prefer to have exclusive control over development in all geographies or indications within a field. Even if we are successful in our efforts to establish new collaborations, the terms that we agree upon may not be favorable to us, and we may not be able to maintain such collaborations if, for example, development or approval of a product candidate is delayed or sales of an approved product are disappointing. Any inability or delay in entering into new research and development agreements related to our product candidates, in particular in foreign countries where we do not have and do not intend to establish significant capabilities, could delay the development and commercialization of our product candidates or other product candidates using our technology and reduce their market potential.

We may not realize the benefits of any acquisitions, in-licenses, out-licenses or strategic alliances that we enter into.

We have entered into in-license agreements with multiple licensors and in the future may seek and form our-licenses, strategic alliances, create joint ventures or collaborations, or enter into acquisitions or additional licensing arrangements with third parties that we believe will complement or augment our existing technologies and product candidates.

These transactions can entail numerous operational and financial risks, including exposure to unknown liabilities, disruption of our business and diversion of our management's time and attention in order to manage a collaboration or develop acquired products, product candidates or technologies, incurrence of substantial debt or dilutive issuances of equity securities to pay transaction consideration or costs, higher than expected collaboration, acquisition or integration costs, write-downs of assets or goodwill or impairment charges, increased amortization expenses, difficulty and cost in facilitating the collaboration or combining the operations and personnel of any acquired business, impairment of relationships with key suppliers, manufacturers or customers of any acquired business due to changes in management and ownership and the inability to retain key employees of any acquired business. As a result, we may not be able to realize the benefits of such existing or future acquisitions or in-licenses if we are unable to successfully integrate them into our operations and company culture. Following a strategic transaction or license, we may not achieve the revenue or specific net income that justifies such transaction or such other benefits that led us to enter into the arrangement.

Risks Related to Our Industry and Business Operations

Budget constraints have in the past and may in the future force us to delay our efforts to develop certain product candidates in favor of developing others, which prevents us from commercializing all product candidates as quickly as possible.

Because we are a small company with limited resources, and because research and development is an expensive process, we must regularly assess the most efficient allocation of our research and development budget. As a result, we have been forced to prioritize development activities with the result that we will not be able to fully realize the value of some of our product candidates in a timely manner, as they will be delayed in reaching the market, if at all. For example, in October 2022, we engaged in a strategic reprioritization of our pipeline in an effort to increase our efficiencies. If we are not successful in increasing our efficiency as a result of this strategic reprioritization, our efforts to develop and commercialize our product candidates may be delayed or halted.

Our reprioritization and the associated headcount reduction may not result in anticipated savings, could result in total costs and expenses that are greater than expected and could disrupt our business.

In October 2022, we undertook a reprioritization that reduced our workforce. This reduction in force was completed in the fourth quarter of 2022.

We may incur additional expenses not currently contemplated due to events associated with the reductions in force, for example, the reduction in force may have a future impact on other areas of our liabilities and obligations, including reductions in lease obligations prior to expiration of lease terms, which could result in losses in future periods. We may not realize, in full or in part, the anticipated benefits and savings from this reprioritization and reduction in force due to unforeseen difficulties, delays or unexpected costs. If we are unable to realize the expected operational efficiencies and cost savings from the reduction in force, our operating results and financial condition would be adversely affected. In addition, we may need to undertake restructuring activities or workforce reductions in the future. Furthermore, our initiatives to re-balance our cost structure, including the reduction in force, may be disruptive to our operations. For example, our workforce reduction could yield unanticipated consequences, such as attrition beyond planned staff reductions, increased difficulties in our day-to-day operations and reduced employee morale. If employees who were not affected by the reductions in force seek alternative employment, this could result in us seeking contractor support at unplanned additional expense or harm our productivity. Our workforce reduction could also harm our ability to attract and retain qualified management, scientific, clinical, and manufacturing personnel who are critical to our business. Any failure to attract or retain qualified personnel could prevent us from successfully commercializing our product or developing our potential product candidates, which would adversely affect our business.

As a result of the headcount reduction initiated in connection with our strategic reprioritization, we may experience difficulties in managing our current and any future reprioritizations.

Future growth would impose significant added responsibilities on members of management, including the need to identify, recruit, maintain and integrate additional employees. Due to our limited resources, we may not be able to effectively manage our operations or recruit and retain qualified personnel, which may result in weaknesses in our infrastructure and operations, risks that we may not be able to comply with legal and regulatory requirements, and loss of employees and reduced productivity among remaining employees. For example, the workforce reduction may negatively impact our clinical, regulatory, technical operations, and commercial functions, which would have a negative impact on our ability to successfully develop, and ultimately, commercialize our product candidates. Our future financial performance and our ability to develop our product candidates or additional assets will depend, in part, on our ability to effectively manage any future growth or restructuring, as the case may be.

The COVID-19 pandemic could continue to adversely impact our business, including our ongoing and planned clinical trials, supply chain and business development activities.

Since December 2019, COVID-19, a novel strain of coronavirus, has become a global pandemic, which has resulted in travel restrictions, quarantine orders and other restrictions by governments to reduce the spread of the disease. As a result of these orders, many of our general and administrative employees continue to operate on a hybrid schedule of in-office and remote work, which has impacted certain of our operations and may continue to do so over the long term. We may experience further limitations on employee resources in the future, including because of sickness of employees or their families. The effects of government actions and our own policies and those of third parties to reduce the spread of COVID-19 may negatively impact productivity and slow down or delay our ongoing and future clinical trials, preclinical studies and research and development activities, and may cause disruptions to our supply chain and impair our ability to execute our business development strategy. In the event that government authorities were to enhance current restrictions, our employees who currently are not operating remotely, including but not limited to our lab employees, may no longer be able to access our facilities, and our operations may be further limited or curtailed.

As COVID-19 continues to spread and new variants of the virus emerge, we may experience ongoing disruptions that could severely impact our business, preclinical studies and clinical trials, including:

- interruption or delays in our operations, which may impact our ability to conduct and produce preclinical results required for submission of an IND;
- delays in receiving authorizations from local regulatory authorities to initiate our planned clinical trials;
- delays or difficulties in enrolling patients in our clinical trials due to patients' concerns of contracting COVID-19 while visiting hospitals, including patients with cancer who may be immunocompromised during the COVID-19 pandemic;
- delays or difficulties in clinical site initiation, including difficulties in recruiting clinical site investigators and clinical site staff;
- delays in clinical sites receiving the supplies and materials needed to conduct our clinical trials, including interruption in global shipping that may affect the transport of clinical trial materials;
- changes in local regulations as part of a response to COVID-19 which may require us to change the ways in which our clinical trials are conducted, which may result in unexpected costs, or to discontinue the clinical trials altogether;
- diversion of healthcare resources away from the conduct of clinical trials, including the diversion of hospitals serving as our clinical trial sites and hospital staff supporting the conduct of our clinical trials;
- interruption of key clinical trial activities, such as clinical trial site monitoring, due to limitations on travel imposed or recommended by federal or state governments, employers and others, or interruption of clinical trial subject visits and study procedures, the occurrence of which could affect the integrity of clinical trial data;

- interruption or delays in the operations of the FDA or other regulatory authorities, which may impact review and approval timelines;
- risk that participants enrolled in our clinical trials will contract COVID-19 while the clinical trial is ongoing, which could impact the results of the clinical trial, including by increasing the number of observed adverse events; and
- refusal of the FDA to accept data from clinical trials in affected geographies outside the United States.

These and other disruptions in our operations and the global economy could negatively impact our business, operating results and financial condition.

Our clinical trials have been, and may in the future be, affected by the COVID-19 pandemic. For example, some of our clinical trial sites in the United States and Australia slowed down or temporarily suspended enrollment of new patients, denied access to site monitors and otherwise curtailed certain operations. Similarly, our ability to recruit and retain principal investigators and site staff who, as healthcare providers, may have heightened exposure to COVID-19, may be adversely impacted. Our ongoing or planned clinical trials may also be impacted by interruptions or delays in the operations of the FDA, NMPA, EMA or comparable foreign regulatory authorities. We and our CROs have also made certain adjustments to the operation of our trials in an effort to ensure compliance with GCP, to assure the safety of trial participants, and to minimize risks to trial integrity during the pandemic in accordance with the guidance issued by the FDA and may need to make further adjustments in the future. Many of these adjustments are new and untested, may not be effective, and may have unforeseen effects on the enrollment, progress and completion of these trials and the findings from these trials. These events could delay our clinical trials, increase the cost of completing our clinical trials and negatively impact the integrity, reliability or robustness of the data from our clinical trials.

In addition, quarantines, shelter-in-place and similar government orders, or the perception that such orders, shutdowns or other restrictions on the conduct of business operations could occur, related to COVID-19 or other infectious diseases could impact personnel at third-party manufacturing facilities upon which we rely, or the availability or cost of materials, which could disrupt the supply chain for our product candidates. The demand for vaccines and COVID-19 treatments and potential for manufacturing facilities and materials to be commandeered under the Defense Production Act of 1950, or equivalent foreign legislation, may make it more difficult to obtain materials or manufacturing slots for the products needed for our clinical trials which could lead to delays in these trials. To the extent our suppliers and service providers are unable to comply with their obligations under our agreements with them or they are otherwise unable to deliver or are delayed in delivering goods and services to us due to the COVID-19 pandemic or government mandates to participate in COVID-19 vaccine or treatment production, our ability to continue meeting clinical supply demand for our product candidates or otherwise advancing development of our product candidates may become impaired.

The spread of COVID-19 and actions taken to reduce its spread may also materially affect us economically. While the potential economic impact brought by, and the duration of, the COVID-19 pandemic may be difficult to assess or predict, there could be a significant disruption of global financial markets, reducing our ability to access capital, which could in the future negatively affect our liquidity and financial position. In addition, the trading prices for other biologics companies have been highly volatile as a result of the COVID-19 pandemic. As a result, we may face difficulties raising capital through sales of our ordinary shares.

COVID-19 and actions taken to reduce its spread continue to rapidly evolve. The extent to which COVID-19 may impede the development of our product candidates, reduce the productivity of our employees, disrupt our supply chains, delay our clinical trials, reduce our access to capital or limit our business development activities, will depend on future developments, which are highly uncertain and cannot be predicted with confidence. To the extent the COVID-19 pandemic adversely affects our business and financial results, it may also have the effect of heightening many of the other risks described in “*Item 1A. Risk Factors*” and elsewhere in this Annual Report, such as those relating to the timing and results of our clinical trials and our financing needs.

Our employees, principal investigators, consultants and commercial partners may engage in misconduct or other improper activities, including non-compliance with regulatory standards and requirements and insider trading.

We are exposed to the risk of fraud or other misconduct by our employees, principal investigators, consultants and commercial partners. Misconduct by these parties could include intentional failures to comply with the regulations of the FDA and non-U.S. regulators, provide accurate information to the FDA and non-U.S. regulators, comply with healthcare fraud and abuse laws and regulations in the United States and abroad, report financial information or data accurately or disclose unauthorized activities to us. In particular, sales, marketing and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, misconduct, kickbacks, self-dealing and other abusive practices. These laws and regulations may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. Such misconduct could also involve the improper use of information obtained in the course of clinical trials, which could result in regulatory sanctions and cause serious harm to our reputation. It is not always possible to identify and deter employee misconduct, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to comply with these laws or regulations. If any such actions are instituted against us those actions could have a significant impact on our business, including the imposition of significant civil, criminal and administrative penalties, damages, fines, disgorgement, imprisonment, exclusion from government funded healthcare programs, such as Medicare and Medicaid, contractual damages, reputational harm, diminished profits and future earnings, additional reporting obligations and oversight if subject to a corporate integrity agreement or other agreement to resolve allegations of non-compliance with these laws, and the curtailment or restructuring of our operations.

We face potential product liability, and, if successful claims are brought against us, we may incur substantial liability and costs. If the use of our product candidates harms patients or is perceived to harm patients even when such harm is unrelated to our product candidates, our regulatory approvals could be revoked or otherwise negatively impacted and we could be subject to costly and damaging product liability claims.

The use of our product candidates in clinical trials and the sale of any products for which we obtain marketing approval exposes us to the risk of product liability claims. Product liability claims might be brought against us by consumers, healthcare providers, pharmaceutical companies or others selling or otherwise coming into contact with our products. Our product candidates may induce adverse events or SAEs, including but not limited to death and ocular toxicity. If we cannot successfully defend against product liability claims, we could incur substantial liability and costs. In addition, regardless of merit or eventual outcome, product liability claims may result in:

- impairment of our business reputation;
- withdrawal of clinical trial participants;
- costs due to related litigation;
- distraction of management's attention from our primary business;
- substantial monetary awards to patients or other claimants;
- the inability to commercialize our product candidates; and
- decreased demand for our product candidates, if approved for commercial sale.

We believe our product liability insurance coverage is sufficient in light of our current clinical programs; however, we may not be able to maintain insurance coverage at a reasonable cost or in sufficient amounts to protect us against losses due to liability. If we obtain marketing approval for product candidates, we intend to expand our insurance coverage to include the sale of commercial products; however, we may be unable to obtain product liability insurance on commercially reasonable terms or in adequate amounts. On occasion, large judgments have been awarded in class action lawsuits based on drugs or medical treatments that had unanticipated adverse effects. A successful product liability claims, or series of claims brought against us could cause our share price to decline and, if judgments exceed our insurance coverage, could adversely affect our results of operations and business.

Patients with cancer are often already in severe and advanced stages of disease and have both known and unknown significant pre-existing and potentially life-threatening health risks. These patients are also currently on or have recently been on multiple other therapies for their cancer or other underlying conditions. During the course of treatment in our clinical trials, patients may suffer adverse events, including death, for reasons that may be related to our product candidates. Such events could subject us to costly litigation, require us to pay substantial amounts of money to injured patients, delay, negatively impact or end our opportunity to receive or maintain regulatory approval to market our product candidates, or require us to suspend or abandon our commercialization efforts. Even in a circumstance in which we do not believe that an adverse event is related to our product candidates, the investigation into the circumstance may be time-consuming or inconclusive. These investigations may interrupt our development efforts, delay our regulatory approval process, or limit the type of regulatory approvals our product candidates receive or maintain. As a result of these factors, a product liability claim, even if successfully defended, could have a material adverse effect on our business, financial condition or results of operations.

We are highly dependent on our key personnel, and if we are not successful in attracting and retaining highly qualified personnel, we may not be able to successfully implement our business strategy.

Our ability to compete in the highly competitive biotechnology and pharmaceutical industries depends upon our ability to attract and retain highly qualified directors and managerial, scientific and medical personnel. We are highly dependent on our management, scientific and medical personnel.

We conduct substantial operations at our facilities in San Diego. This region is headquarters to many other biologics companies and many academic and research institutions. Competition for skilled personnel in our market is intense and may limit our ability to hire and retain highly qualified personnel on acceptable terms or at all.

To induce valuable employees to remain at our company, in addition to salary and cash incentives, we have provided share options that vest over time. The value to employees of share options that vest over time may be significantly affected by movements in our share price that are beyond our control and may at any time be insufficient to counteract more lucrative offers from other companies. Despite our efforts to retain valuable employees, members of our management, scientific and development teams may terminate their employment with us on short notice. Although we have employment agreements with certain of our key employees, these employment agreements provide for at-will employment, which means that any of our employees could leave our employment at any time, with or without notice. For example, we have had several leadership and management transitions in 2021 and 2022. The loss of the services of any of our executive officers, key employees, and scientific and medical advisors, and our inability to find suitable replacements could result in delays in product development and harm our business. We do not maintain “key person” insurance policies on the lives of these individuals or the lives of any of our employees. Our success also depends on our ability to continue to attract, retain and motivate highly skilled junior, mid-level and senior managers as well as junior, mid-level and senior scientific and medical personnel.

We may experience a disruption of our business activities due to senior executive transitions.

Recently hired executives may view the business differently than prior members of management, and over time may make changes to our strategic focus, operations, business plans, existing personnel and their responsibilities. We may not be able to properly manage such shift in focus, and any changes to our business may not ultimately prove successful.

In addition, we have had several leadership and management transitions in 2021 and 2022. Leadership transitions and management changes can be inherently difficult to manage and may cause uncertainty or a disruption to our business or may increase the likelihood of turnover in key officers and employees. Our success depends in part on having a successful leadership team. If we cannot effectively manage leadership transitions and management changes, it could make it more difficult to successfully operate our business and pursue our business goals. We may not be able to retain the services of any of our current executives or other key employees. If we do not succeed in attracting well-qualified employees, retaining and motivating existing employees or integrating new executives and employees, our business could be materially and adversely affected.

We expect to expand our development, regulatory and operational capabilities and, as a result, we may encounter difficulties in managing our growth, which could disrupt our operations.

As of December 31, 2022, we had 66 employees. As we advance our research and development programs, we will be required to further increase the number of our employees and the scope of our operations, particularly in the areas of clinical development, quality, regulatory affairs and, if any of our product candidates receives marketing approval, sales, marketing and distribution. To manage any future growth, we must:

- identify, recruit integrate, maintain and motivate additional qualified personnel;
- manage our development efforts effectively, including the initiation and conduct of clinical trials for our product candidates, both as monotherapy and in combination with other therapeutics; and
- improve our operational, financial and management controls, reporting systems and procedures.

Our future financial performance and our ability to develop, manufacture and commercialize our product candidates, if approved, will depend, in part, on our ability to effectively manage any future growth, and our management may also have to divert financial and other resources, and a disproportionate amount of its attention away from day-to-day activities in order to devote a substantial amount of time, to managing these growth activities.

If we are not able to effectively expand our organization by hiring new employees and expanding our groups of consultants and contractors, we may not be able to successfully implement the tasks necessary to further develop and commercialize our product candidates and, accordingly, may not achieve our research, development and commercialization goals.

Our business operations and current and future relationships with investigators, healthcare professionals, consultants, third-party payors and customers are subject, directly or indirectly, to federal and state healthcare fraud and abuse laws, transparency laws and other healthcare laws and regulations. If we are unable to comply, or have not fully complied, with such laws, we could face substantial penalties.

Although we do not currently have any products on the market, our operations may be, directly or indirectly through our prescribers, customers and third-party payors, subject to various U.S. federal and state healthcare laws and regulations, including, without limitation, the U.S. federal Anti-Kickback Statute, the U.S. federal civil and criminal false claims laws and the Physician Payments Sunshine Act and regulations. Healthcare providers and others play a primary role in the recommendation and prescription of any products for which we obtain marketing approval. These laws may impact, among other things, our current business operations, including our clinical research activities, and proposed sales, marketing and education programs and constrain the business of financial arrangements and relationships with healthcare providers and other parties through which we may market, sell and distribute our products for which we obtain marketing approval. In addition, we may be subject to additional healthcare, statutory and regulatory requirements and enforcement by foreign regulatory authorities in jurisdictions in which we conduct our business. The laws that may affect our ability to operate include:

- the U.S. federal Anti-Kickback Statute, which prohibits, among other things, persons or entities from knowingly and willfully soliciting, offering, receiving or paying any remuneration (including any kickback, bribe or certain rebates), directly or indirectly, overtly or covertly, in cash or in kind, to induce or reward either the referral of an individual for, or the purchase, lease, order or recommendation of, any good, facility, item or service, for which payment may be made, in whole or in part, under U.S. federal and state healthcare programs such as Medicare and Medicaid. The government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the federal civil False Claims Act or federal civil money penalties statute. This statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on the one hand, and prescribers, purchasers, and formulary managers on the other. Although there are several statutory exceptions and regulatory safe harbors protecting certain common activities from prosecution, they are drawn narrowly, and practices that involve remuneration intended to induce prescribing, purchasing or recommending may be subject to scrutiny if they do not qualify for an exception or safe harbor. A person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation;

- the U.S. federal false claims, including the False Claims Act, which can be enforced through whistleblower actions, and civil monetary penalties laws, which, among other things, impose criminal and civil penalties against individuals or entities for knowingly presenting, or causing to be presented, to the U.S. federal government, claims for payment or approval that are false or fraudulent, knowingly making, using or causing to be made or used, a false record or statement material to a false or fraudulent claim, or from knowingly making a false statement to avoid, decrease or conceal an obligation to pay money to the U.S. federal government. Manufacturers can be held liable under the False Claims Act even when they do not submit claims directly to government payors if they are deemed to “cause” the submission of false or fraudulent claims. Companies that submit claims directly to payors may also be liable under the False Claims Act for the direct submission of such claims. The False Claims Act also permits a private individual acting as a “whistleblower” to bring actions on behalf of the federal government alleging violations of the False Claims Act and to share in any monetary recovery. In addition, the government may assert that a claim including items and services resulting from a violation of the U.S. federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the False Claims Act;
- the U.S. federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which imposes criminal and civil liability for, among other things, knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program, or knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false statement, in connection with the delivery of, or payment for, healthcare benefits, items or services; similar to the U.S. federal Anti-Kickback Statute, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation;
- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009, or HITECH, and their respective implementing regulations, impose requirements on certain covered healthcare providers, health plans, and healthcare clearinghouses and their respective business associates that perform services for them that involve the use, or disclosure of, individually identifiable health information as well as their covered subcontractors, relating to the privacy, security, and transmission of such individually identifiable health information. HITECH also created new tiers of civil monetary penalties, amended HIPAA to make civil and criminal penalties directly applicable to business associates, and gave state attorneys general new authority to file civil actions for damages or injunctions in federal courts to enforce the federal HIPAA laws and seek attorneys’ fees and costs associated with pursuing federal civil actions;
- the U.S. Federal Food, Drug and Cosmetic Act, which prohibits, among other things, the adulteration or misbranding of drugs, biologics and medical devices;
- the U.S. federal legislation commonly referred to as Physician Payments Sunshine Act, enacted as part of the ACA, and its implementing regulations, which requires certain manufacturers of drugs, devices, biologics and medical supplies that are reimbursable under Medicare, Medicaid or the Children’s Health Insurance Program to report annually to the CMS information related to certain payments and other transfers of value to physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors), other healthcare professionals (such as physician assistants and nurse practitioners) and teaching hospitals, as well as ownership and investment interests held by the physicians described above and their immediate family members;
- analogous state laws and regulations, including: state anti-kickback and false claims laws, which may apply to our business practices, including, but not limited to, research, distribution, sales and marketing arrangements and claims involving healthcare items or services reimbursed by any third-party payor, including private insurers; state laws that require pharmaceutical companies to comply with the pharmaceutical industry’s voluntary compliance guidelines and the relevant compliance guidance promulgated by the U.S. federal government, or otherwise restrict payments that may be made to healthcare providers and other potential referral sources; state laws and regulations that require drug manufacturers to file reports relating to pricing and marketing information, which requires tracking gifts and other remuneration and items of value provided to healthcare professionals and entities; and state and local laws requiring the registration of pharmaceutical sales representatives; and

- European and other foreign law equivalents of each of the laws, including reporting requirements detailing interactions with and payments to healthcare providers.

Additionally, as further discussed below, on November 20, 2020, the Department of Health and Human Services, or HHS, finalized a regulation modifying the federal Anti-Kickback Statute regulatory safe harbors that, among other things, (i) removed safe harbor protection for certain price reductions from pharmaceutical manufacturers, and (ii) created new a safe harbor for certain fixed fee arrangements between pharmacy benefit managers and manufacturers.

Ensuring that our internal operations and future business arrangements with third parties comply with applicable healthcare laws and regulations will involve substantial costs. It is possible that governmental authorities will conclude that our business practices do not comply with current or future statutes, regulations, agency guidance or case law involving applicable fraud and abuse or other healthcare laws and regulations. If our operations are found to be in violation of any of the laws described above or any other governmental laws and regulations that may apply to us, we may be subject to significant penalties, including civil, criminal and administrative penalties, damages, fines, exclusion from U.S. government funded healthcare programs, such as Medicare and Medicaid, or similar programs in other countries or jurisdictions, disgorgement, imprisonment, contractual damages, reputational harm, diminished profits, additional reporting requirements and oversight if we become subject to a corporate integrity agreement or similar agreement to resolve allegations of non-compliance with these laws and the delay, reduction, termination or restructuring of our operations. Further, defending against any such actions can be costly and time-consuming, and may require significant financial and personnel resources. Therefore, even if we are successful in defending against any such actions that may be brought against us, our business may be impaired. If any of the physicians or other providers or entities with whom we expect to do business is found to not be in compliance with applicable laws, they may be subject to significant criminal, civil or administrative sanctions, including exclusions from government funded healthcare programs and imprisonment. If any of the above occur, it could adversely affect our ability to operate our business and our results of operations.

Enacted and future legislation may increase the difficulty and cost for us to obtain marketing approval of and commercialize our product candidates and affect the prices we may charge for such product candidates.

The United States and many foreign jurisdictions have enacted or proposed legislative and regulatory changes affecting the healthcare system that could prevent or delay marketing approval of our product candidates, restrict or regulate post-approval activities and affect our ability to profitably sell any product for which we obtain marketing approval.

In March 2010, the ACA was enacted, which substantially changed the way health care is financed by both governmental and private insurers, and significantly impacts the U.S. pharmaceutical industry. The ACA, among other things, increased the minimum Medicaid rebates owed by manufacturers under the Medicaid Drug Rebate Program and extended the rebate program to individuals enrolled in Medicaid managed care organizations, established annual fees and taxes on manufacturers of certain branded prescription drugs, and promoted a new Medicare Part D coverage gap discount program.

Since its enactment, there have been and there remain executive, judicial and congressional challenges to certain aspects of the ACA. As a result, there have been delays in the implementation of, and action taken to repeal or replace, certain aspects of the ACA. For example, since January 2017, former President Trump signed several Executive Orders designed to delay the implementation of certain provisions of the ACA or otherwise circumvent some of the requirements for health insurance mandated by the ACA. While Congress has not passed comprehensive repeal legislation to date, it has enacted laws that modify certain provisions of the ACA such as the Tax Cuts and Jobs Act of 2017, or TCJA, which decreased the “individual mandate” to \$0. On June 17, 2021, the U.S. Supreme Court dismissed the most recent judicial challenge to the ACA brought by several states without specifically ruling on the constitutionality of the ACA. Further, on August 16, 2022, President Biden signed the Inflation Reduction Act of 2022, or IRA, into law, which among other things, extends enhanced subsidies for individuals purchasing health insurance coverage in ACA marketplaces through plan year 2025. The IRA also eliminates the “donut hole” under the Medicare Part D program beginning in 2025 by significantly lowering the beneficiary maximum out-of-pocket cost and creating a new manufacturer discount program. It is possible that the ACA will be subject to judicial or congressional challenges in the future. It is unclear how such challenges and the healthcare reform measures of

the Biden administration, will impact the ACA or our business. We continue to evaluate the effect that the ACA and its possible repeal and replacement has on our business.

In addition, other legislative changes have been proposed and adopted since the ACA was enacted. For example, in August 2011, the Budget Control Act of 2011 was signed into law, which, among other things, included aggregate reductions to Medicare payments to providers of, on average, 2% per fiscal year until 2031, unless Congress takes additional action. Under current legislation the actual reduction in Medicare payments will vary from 1% in 2022 to up to 4% in the final fiscal year of this sequester.

Recently, there has been increasing legislative and enforcement interest in the United States with respect to specialty drug pricing practices. Specifically, there have been several recent U.S. congressional inquiries and legislation designed to, among other things, bring more transparency to drug pricing, reduce the cost of prescription drugs under Medicare, review the relationship between pricing and manufacturer patient programs and reform government program reimbursement methodologies for drugs. In addition, there have been several changes to the 340B drug pricing program, which imposes ceilings on prices that drug manufacturers can charge for medications sold to certain healthcare facilities. Some of these changes are undergoing legal challenges, and their status is currently in question. It is unclear how these developments could affect covered hospitals who might purchase our future products and affect the rates we may charge such facilities for our approved products in the future, if any.

Additionally, in July 2021, the Biden administration released an executive order, “Promoting Competition in the American Economy,” with multiple provisions aimed at prescription drugs. In response to President Biden’s executive order, on September 9, 2021, HHS released a Comprehensive Plan for Addressing High Drug Prices that outlines principles for drug pricing reform and sets out a variety of potential legislative policies that Congress could pursue to advance these principles. Further, the IRA, among other things (i) directs HHS to negotiate the price of certain high-expenditure, single-source drugs and biologics covered under Medicare and (ii) imposes rebates under Medicare Part B and Medicare Part D to penalize price increases that outpace inflation. These provisions will take effect progressively starting in fiscal year 2023, although they may be subject to legal challenges. Additionally, the Biden administration released an additional executive order on October 14, 2022, directing HHS to report on how the Center for Medicare and Medicaid Innovation can be further leveraged to test new models for lowering drug costs for Medicare and Medicaid beneficiaries. We expect that Congress will continue to seek new legislative measures to control drug costs. Any reduction in reimbursement from Medicare and other government programs may result in a similar reduction in payments from private payers. At the state level, legislatures have increasingly passed legislation and implemented regulations designed to control costs of pharmaceutical and biological products. Moreover, regional healthcare authorities and individual hospitals are increasingly using bidding procedures to determine what pharmaceutical products and which suppliers will be included in their prescription drug and other healthcare programs.

We expect that the healthcare reform measures that have been adopted, and that may be adopted in the future, may result in more rigorous coverage criteria and in additional downward pressure on the price that we receive for any approved product and could seriously harm our future revenues. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private payors. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability or commercialize our products.

Our product candidates are subject to government price controls in certain jurisdictions that may affect our revenue.

There has been heightened governmental scrutiny in the United States, China, the European Union, Japan and other jurisdictions of pharmaceutical pricing practices in light of the rising cost of prescription drugs. In the United States, such scrutiny has resulted in several recent Congressional inquiries and proposed and enacted federal legislation designed to, among other things, bring more transparency to product pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for products. At the federal level, Congressional leadership and the Biden administration have each indicated that they will continue to seek new legislative and/or administrative measures to control drug costs. At the state level, legislatures have increasingly enacted legislation and implemented regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on

certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing. Outside of the United States, particularly in the European Union, the pricing of prescription pharmaceuticals is subject to governmental control. In these countries, pricing negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a product. To obtain coverage and reimbursement or pricing approval in some countries, we may be required to conduct a clinical trial that compares the cost-effectiveness of our product candidate to other available therapies. If reimbursement of our products is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our business could be harmed.

We are subject to stringent and evolving federal, state, local and foreign laws, regulations, rules, contractual obligations, policies, industry standards, and other obligations relating to privacy and data protection laws. Our actual or perceived failure to comply with such obligations could lead to government enforcement actions (which could include civil or criminal penalties), private litigation, and/or adverse publicity and could negatively affect our operating results and business.

In the ordinary course of business, we collect, receive, store, process, generate, use, transfer, disclose, make accessible, protect, secure, dispose of, transmit, and share (collectively, process) personal data and other sensitive information, including proprietary and confidential business data, trade secrets, intellectual property, data we collect about trial participants in connection with clinical trials, and sensitive third-party data. Additionally, we may obtain health information from third parties (including research institutions from which we obtain clinical trial data). Therefore, we and our collaborators and third-party providers may be subject to federal, state, local and foreign data privacy and security obligations, such as various laws, regulations, guidance, industry standards, external and internal privacy and security policies, contractual requirements, and other obligations relating to data privacy and security. In the United States, numerous federal, state, and local laws and regulations, including federal health information privacy laws, state data breach notification laws, state health information privacy laws, federal and state consumer protection laws (e.g., Section 5 of the Federal Trade Commission Act), and other similar laws (e.g., wiretapping laws) that govern the processing of health-related and other personal information could apply to our operations or the operations of our collaborators and third-party providers. For example, HIPAA imposes specific requirements relating to the privacy, security, and transmission of individually identifiable health information.

Furthermore, California enacted the California Consumer Privacy Act, or the CCPA, which applies to personal information of California consumers, business representatives, and employees, and gives California residents expanded rights to access and delete their personal information, opt out of certain personal information sharing and receive detailed information about how their personal information is used. The CCPA provides for civil penalties for violations, as well as a private right of action for data breaches. Although the CCPA exempts some data processed in the context of clinical trials, the CCPA increases compliance costs and potential liability with respect to other personal data we maintain about California residents. In addition, the California Privacy Rights Act of 2020 expands the CCPA's requirements, including by adding a new right for individuals to correct their personal information and establishing a new regulatory agency to implement and enforce the law. Other states, such as Virginia and Colorado, have also passed comprehensive privacy laws, and similar laws are being considered in several other states, as well as the federal and local levels. While these states, like the CCPA, also exempt some data processed in the context of clinical trials, these developments further complicate compliance efforts, and increase legal risk and compliance costs for us and the third parties upon whom we rely.

An increasing number of foreign data protection laws, regulations, and industry standards, including the European Union's General Data Protection Regulation, or EU GDPR, the United Kingdom's GDPR, or UK GDPR (EU and UK GDPR collectively, GDPR), and China's Personal Information Protection Law, or PIPL, may also apply to health-related and other personal information obtained from individuals outside of the United States. For example, the EU GDPR, which came into effect on May 25, 2018, imposes strict requirements for processing the personal data of individuals within the European Economic Area, or EEA, including health-related data, as well as potential fines for noncompliant companies of up to the greater of €20 million or 4% of annual global revenue. In addition, under the EU GDPR, companies may face private litigation related to processing of personal data brought by classes of data subjects or consumer protection organizations authorized at law to represent their interests. We also have operations in China and may be subject to new and emerging data privacy regimes in Asia,

including China's Cyber Security Law, the Measures for the Management of Scientific Data, Regulation on the Administration of Human Genetic Resources, and PIPL.

In addition, we may be unable to transfer personal data from Europe (including the EEA and UK) and other jurisdictions to the United States or other countries due to data localization requirements or limitations on cross-border data flows. Europe and other jurisdictions have enacted laws requiring data to be localized or limiting the transfer of personal data to other countries. In particular, the EEA and UK have significantly restricted the transfer of personal data to the United States and other countries whose privacy laws it believes are inadequate. Other jurisdictions may adopt similarly stringent interpretations of their data localization and cross-border data transfer laws. Although there are currently various mechanisms that may be used to transfer personal data from the EEA and UK to the United States in compliance with law, such as the EEA and UK's standard contractual clauses, these mechanisms are subject to legal challenges, and we may not be able to satisfy or rely on these measures to lawfully transfer personal data to the United States. If there is no lawful manner for us to transfer personal data from the EEA, the UK, or other jurisdictions to the United States, or if the requirements for a legally-compliant transfer are too onerous, we could face significant adverse consequences, including the interruption or degradation of our operations, the need to relocate part of or all of our business or data processing activities to other jurisdictions at significant expense, increased exposure to regulatory actions, substantial fines and penalties, the inability to transfer data and work with partners, vendors and other third parties, and injunctions against our processing or transferring of personal data necessary to operate our business. Additionally, companies that transfer personal data out of the EEA and UK to other jurisdictions, particularly to the United States, are subject to increased scrutiny from regulators, individual litigants, and activities groups. Some European regulators have ordered certain companies to suspend or permanently cease certain transfers of personal data out of EU for allegedly violating the GDPR's cross-border data transfer limitations.

In addition to data privacy and security laws, we are contractually subject to industry standards adopted by industry groups and may become subject to such obligations in the future. We are also bound by other contractual obligations related to data privacy and security, and our efforts to comply with such obligations may not be successful. Moreover, clinical trial subjects about whom we or our potential collaborators obtain information, as well as the providers who share this information with us, may contractually limit our ability to use and disclose such information.

We publish privacy policies, marketing materials, and other statements regarding data privacy and security. If these policies, materials or statements are found to be deficient, lacking in transparency, deceptive, unfair, or misrepresentative of our practices, we may be subject to investigation, enforcement actions by regulators, or other adverse consequences.

Obligations related to data privacy and security are quickly changing, becoming increasingly stringent, and creating regulatory uncertainty. Additionally, these obligations may be subject to differing applications and interpretations, which may be inconsistent or conflict among jurisdictions. Preparing for and complying with these obligations requires us to devote significant resources and may necessitate changes to our services, information technologies, systems, and practices and to those of any third parties that process personal data on our behalf.

We may at times fail (or be perceived to have failed) in our efforts to comply with our data privacy and security obligations. Moreover, despite our efforts, our personnel, collaborators, or third-party providers may fail to comply with such obligations, which could negatively impact our business operations. If we or our collaborators and third-party providers fail to comply with applicable data privacy and security obligations, we could face significant consequences, including but not limited to government enforcement actions (which could include investigations, fines, audits, inspections, civil or criminal penalties), private litigation (including class-action claims), additional reporting requirements and/or oversight, bans on processing personal data, orders to destroy or not use personal data, and/or adverse publicity and could negatively affect our operating results and business. Claims that we have violated individuals' privacy rights, or otherwise failed to comply with data protection laws or other obligations, even if we are not found liable, could be expensive and time consuming to defend, could result in adverse publicity and could have a material adverse effect on our business, financial condition, results of operations and prospects.

We or the third parties upon whom we depend may be adversely affected by earthquakes, fires or other natural disasters and our business continuity and disaster recovery plans may not adequately protect us from a serious disaster.

Our headquarters and main research facility are located in San Diego, California, which in the past has experienced severe earthquakes and fires. If these earthquakes, fires, other natural disasters, terrorism and similar unforeseen events beyond our control prevented us from using all or a significant portion of our headquarters or research facility, it may be difficult or, in certain cases, impossible for us to continue our business for a substantial period of time. We do not have a disaster recovery or business continuity plan in place and may incur substantial expenses as a result of the absence or limited nature of our internal or third-party service provider disaster recovery and business continuity plans, which, particularly when taken together with our lack of earthquake insurance, could have a material adverse effect on our business. Furthermore, integral parties in our supply chain are operating from single sites, increasing their vulnerability to natural disasters or other sudden, unforeseen and severe adverse events. If such an event were to affect our supply chain, it could have a material adverse effect on our ability to conduct our clinical trials, our development plans and business.

The United States and Chinese tax authorities may disagree with our conclusions regarding certain tax positions, resulting in unanticipated costs, taxes or non-realization of expected benefits.

As of December 31, 2022, we held capital resources in our subsidiaries, Shanghai Ambrx Biopharma Company Limited, or Ambrx Shanghai, and Biolaxy Pharmaceutical Hong Kong Limited, or Ambrx HK. We may decide to repatriate those resources held in such entities, which may include initiating a voluntary liquidation of such entities. In addition, we would need to engage legal and tax specialists to analyze the effects of various structures to the voluntary liquidation and selected a structure that minimized the timeline to completion and maximized the value of the capital resources that could be repatriated in the process. In the event that the United States or Chinese tax authorities do not agree with our analysis, we may be subject to a material tax liability and/or fail to realize the expected benefits of such liquidation. In addition, we may incur additional costs associated with defending our position. Such tax liability and increase in costs may have a material adverse effect on our financial results. Further, the process to repatriate such capital resources may be lengthy and timing consuming and may divert management's attention, the result of which could have a material adverse effect on our business, financial condition, results of operations and prospects.

PRC regulations relating to offshore investment activities by PRC residents and enterprises may increase our administrative burden and restrict our overseas and cross-border investment activity. If our PRC resident and enterprise shareholders fail to make any required applications and filings under such regulations, we may be unable to distribute profits to such shareholders and may become subject to liability under PRC law.

In July 2014, PRC State Administration of Foreign Exchange, or SAFE, promulgated the Circular on Relevant Issues Concerning Foreign Exchange Control on Domestic Residents' Offshore Investment and Financing and Roundtrip Investment through Special Purpose Vehicles, or SAFE Circular 37, which replaces the Notice on Relevant Issues Concerning Foreign Exchange Administration for PRC Residents to Engage in Financing and Round-tripping Investment via Overseas Special Purpose, or SAFE Circular 75. SAFE Circular 37 requires PRC residents, including PRC individuals and PRC corporate entities, to register with SAFE or its local branches in connection with their direct or indirect offshore investment activities. SAFE Circular 37 is applicable to our shareholders who are PRC residents and may be applicable to any offshore acquisitions that we may make in the future.

Under SAFE Circular 37, PRC residents who make, or have prior to the implementation of SAFE Circular 37 made, direct or indirect investments in offshore special purpose vehicles, or SPVs, are required to register such investments with SAFE or its local branches. In addition, any PRC resident who is a direct or indirect shareholder of an SPV, is required to update its registration with the local branch of SAFE with respect to that SPV, to reflect any change of basic information or material events. If any PRC resident shareholder of such SPV fails to make the required registration or to update the registration, the subsidiary of such SPV in China may be prohibited from distributing its profits or the proceeds from any capital reduction, share transfer or liquidation to the SPV, and the SPV may also be prohibited from making additional capital contributions into its subsidiaries in China. In February 2015, SAFE promulgated a Notice on Further Simplifying and Improving Foreign Exchange

Administration Policy on Direct Investment, or SAFE Notice 13. Under SAFE Notice 13, applications for foreign exchange registration of inbound foreign direct investments and outbound direct investments, including those required under SAFE Circular 37, shall be filed with qualified banks instead of SAFE. Qualified banks should examine the applications and accept registrations under the supervision of SAFE.

We may not be aware of the identities of all of our beneficial owners who are PRC residents, nor can we compel our beneficial owners to comply with SAFE registration requirements. All shareholders or beneficial owners of ours who are PRC residents or entities may not have completed any required registration under SAFE Circular 37 and any amendment may not be completed in a timely manner, or at all. The failure of our beneficial owners who are PRC residents to register or amend their foreign exchange registrations pursuant to SAFE Circular 37 and subsequent implementation rules, or the failure of future beneficial owners of our company who are PRC residents to comply with the registration procedures set forth in SAFE Circular 37 and subsequent implementation rules, may subject such beneficial owners or Ambrx Shanghai to fines and legal sanctions. Failure to register or comply with relevant requirements may also limit our ability to contribute additional capital to Ambrx Shanghai and limit Ambrx Shanghai's ability to distribute dividends to us. These risks may have a material adverse effect on our business, financial condition and results of operations.

On December 26, 2017, the National Development and Reform Commission, or NDRC, promulgated the Administrative Measures on Overseas Investments, or NDRC Order No. 11, which took effect as of March 1, 2018. According to NDRC Order No. 11, non-sensitive overseas investment projects are subject to record-filing requirements with the local branch of the NDRC. On September 6, 2014, the Ministry of Commerce, or MOFCOM, promulgated the Administrative Measures on Overseas Investments, which took effect as of October 6, 2014. According to this regulation, overseas investments of PRC enterprises that involve non-sensitive countries and regions and non-sensitive industries are subject to record-filing requirements with a local MOFCOM branch. According to the Circular of the State Administration of Foreign Exchange on Issuing the Regulations on Foreign Exchange Administration of the Overseas Direct Investment of Domestic Institutions, which was promulgated by SAFE on July 13, 2009 and took effect on August 1, 2009, PRC enterprises must register for overseas direct investment with a local SAFE branch.

We may not be fully informed of the identities of all our shareholders or beneficial owners who are PRC entities, and all of our shareholders and beneficial owners who are PRC entities may not have completed, or may not complete upon our request, the overseas direct investment procedures under the aforementioned regulations or other related rules in a timely manner, or at all. If they fail to complete such required filings or registrations required by the overseas direct investment regulations, the relevant authorities may order them to suspend or cease the implementation of such investment impose warnings and sanctions on them, require them to make corrections within a specified time, or limit our ability to distribute dividends and proceeds to Ambrx Shanghai and limit Ambrx Shanghai's ability to distribute dividends to us, which may adversely affect our business, financial condition and results of operations.

Further, as these foreign exchange and outbound investment related regulations and their interpretation and implementation have been constantly evolving, it is unclear how these regulations, and any future regulation concerning offshore or cross-border investments and transactions, will be interpreted, amended and implemented by the relevant government authorities. For example, we may be subject to a more stringent review and approval process with respect to our foreign exchange activities, such as remittance of dividends and foreign-currency-denominated borrowings, which may adversely affect our financial condition and results of operations. We may not have complied and may not be able to comply with all applicable foreign exchange and outbound investment related regulations. In addition, if we decide to acquire a PRC domestic company, we or the owners of such company, as the case may be, may not be able to obtain the necessary approvals or complete the necessary filings and registrations required by the PRC foreign exchange regulations. This may restrict our ability to implement our acquisition strategy and could adversely affect our business and prospects.

Risks Related to Our Intellectual Property

If we are unable to obtain and maintain sufficient intellectual property protection for our platform technologies and product candidates, or if the scope of the intellectual property protection is not sufficiently broad, our competitors could develop and commercialize products similar or identical to ours, and our ability to successfully commercialize our products may be adversely affected.

We rely upon a combination of patents, know-how and confidentiality agreements to protect the intellectual property related to our products and technologies and to prevent third parties from copying and surpassing our achievements, thus eroding our competitive position in our market.

Our success depends in large part on our ability to obtain and maintain patent protection for our platform technologies, product candidates and their uses, as well as our ability to operate without infringing the proprietary rights of others. We seek to protect our proprietary position by filing patent applications in the United States and abroad related to our novel discoveries and technologies that are important to our business. Our pending and future patent applications may not result in patents being issued, our issued patents may not afford sufficient protection of our product candidates or their intended uses against competitors, and the patents issued may be infringed, designed around, invalidated by third parties, or may not effectively prevent others from commercializing competitive technologies, products or product candidates.

Obtaining and enforcing patents is expensive and time-consuming, and we may not be able to file and prosecute all necessary or desirable patent applications or maintain and/or enforce patents that may issue based on our patent applications, at a reasonable cost or in a timely manner, including delays as a result of the COVID-19 pandemic impacting us or our licensors' operations, the preparation and prosecution of patent filings performed primarily by our internal team, and/or the increasing financial costs associated with managing a growing patent estate. It is also possible that we will fail to identify patentable aspects of our research and development results before it is too late to obtain patent protection. Although we enter into non-disclosure and confidentiality agreements with parties who have access to patentable aspects of our research and development output, such as our employees, corporate collaborators, outside scientific collaborators, contract research organizations, contract manufacturers, consultants, advisors and other third parties, any of these parties may breach these agreements and disclose such results before a patent application is filed, thereby jeopardizing our ability to seek patent protection. Furthermore, we may not be able to obtain full cooperation from former employees who are listed as inventors on our patents. Although such former employees have assigned their inventions to the company, we may need to periodically consult with such former employees about matters relevant to the inventions disclosed in our patents, and a lack of cooperation from these former employees may not allow us to obtain the broadest possible patent protection for our inventions.

Composition of matter patents for biological and pharmaceutical product candidates often provide a strong form of intellectual property protection for those types of products, as such patents provide protection without regard to any method of use. The claims in our pending patent applications directed to composition of matter of our product candidates may not be considered patentable by the U.S. Patent and Trademark Office, or USPTO, or by patent offices in foreign countries, and the claims in any of our issued patents may not be considered valid and enforceable by courts in the United States or foreign countries. Method of use patents protect the use of a product for the specified method. This type of patent does not prevent a competitor from making and marketing a product that is identical to our product for an indication that is outside the scope of the patented method. Moreover, even if competitors do not actively promote their product for our targeted indications, physicians may prescribe these products "off-label." Although off-label prescriptions may infringe or contribute to the infringement of method of use patents, the practice is common and such infringement is difficult to prevent or prosecute.

The patent position of biologics companies generally is highly uncertain, involves complex legal and factual questions and has in recent years been the subject of much litigation, resulting in court decisions, including Supreme Court decisions, which have increased uncertainties as to the ability to enforce patent rights in the future. In addition, the laws of foreign countries may not protect our rights to the same extent as the laws of the United States, or vice versa.

The patent application process is subject to numerous risks and uncertainties, and we or our potential future collaborators may not be successful in protecting our product candidates by obtaining and defending patents. For example, we may not be aware of all third-party intellectual property rights potentially relating to our product candidates or their intended uses, and as a result the impact of such third-party intellectual property rights upon the patentability of our own patents and patent applications, as well as the impact of such third-party intellectual property upon our freedom to operate, is highly uncertain. Patent applications in the United States and other jurisdictions are typically not published until 18 months after filing or, in some cases, not at all. Therefore, we may not have been the first to make the inventions claimed in our patents or pending patent applications, or the first to file for patent protection of such inventions. As a result, the issuance, inventorship, scope, validity, enforceability and commercial value of our patent rights are highly uncertain. Our pending patent applications may be challenged in patent offices in the United States and abroad. Even issued patents may later be found invalid or unenforceable or may be modified or revoked in proceedings instituted by third parties before various patent offices or in courts. For example, our pending patent applications may be subject to third-party pre-issuance submissions of prior art to the USPTO or our issued patents may be subject to post-grant review, or PGR, proceedings, oppositions, derivations, reexaminations, or *inter partes* review, or IPR, proceedings, in the United States or elsewhere, challenging our patent rights or the patent rights of others. Additionally, if there was relevant “prior art” with respect to our patent applications that was not disclosed to the USPTO, our granted patents could be limited or found invalid. An adverse determination in any such challenges may result in loss of exclusivity or in patent claims being narrowed, invalidated, or held unenforceable, in whole or in part, which could limit our ability to stop others from using or commercializing similar or identical technology and products, or limit the duration of the patent protection of our technology and products. In addition, given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized. The degree of future protection for our proprietary rights is uncertain. Only limited protection may be available and may not adequately protect our rights or permit us to gain or keep any competitive advantage. Any failure to obtain or maintain patent protection with respect to our product candidates or their uses could have a material adverse effect on our business, financial condition, results of operations and prospects.

In addition to the protection afforded by patents, we rely on trade secret protection and confidentiality agreements to protect proprietary know-how that is not patentable, processes for which patents are difficult to enforce and any other elements of our discovery and development processes that involve proprietary know-how, information or technology that is not covered by patents. We may also rely on trade secret protection as temporary protection for concepts that may be included in a future patent filing. However, trade secret protection will not protect us from innovations that a competitor develops independently of our proprietary know-how. If a competitor independently develops a technology that we protect as a trade secret and files a patent application on that technology, then we may not be able to patent that technology in the future, may require a license from the competitor to use our own know-how, and if the license is not available on commercially viable terms, then we may not be able to launch our product. Although we require all of our employees to assign their inventions to us, and require all of our employees, consultants, advisors and any third parties who have access to our proprietary know-how, information or technology to enter into confidentiality agreements, our trade secrets and other confidential proprietary information may nevertheless be disclosed or competitors may otherwise gain access to our trade secrets or independently develop substantially equivalent information and techniques. Furthermore, the laws of some foreign countries do not protect proprietary rights to the same extent or in the same manner as the laws of the United States. As a result, we may encounter significant problems in protecting and defending our intellectual property both in the United States and abroad. If we are unable to prevent unauthorized material disclosure of our intellectual property to third parties, we will not be able to establish or maintain a competitive advantage in our market, and this scenario could materially adversely affect our business, financial condition and results of operations.

Patent rights relating to inventions described and claimed in our pending patent applications may not issue and patents based on our patent applications may be challenged and rendered invalid and/or unenforceable.

The patent application process is subject to numerous risks and uncertainties, and we or our potential future collaborators may not be successful in protecting our product candidates by obtaining and defending patents. We have pending United States and foreign patent applications in our portfolio; however, we cannot predict:

- if and when patents may issue based on our patent applications;
- the scope of protection of any patent issuing based on our patent applications;
- whether the claims of any patent issuing based on our patent applications will provide protection against competitors;
- whether or not third parties will find ways to invalidate or circumvent our patent rights, including designing around our patents;
- whether or not others will obtain patents claiming aspects similar to those covered by our patents and patent applications;
- whether we will need to initiate litigation or administrative proceedings to enforce and/or defend our patent rights which will be costly whether we win or lose; and/or
- whether the patent applications that we own or in-license will result in issued patents with claims that cover our product candidates or uses thereof in the United States or in other foreign countries.

The claims in our pending patent applications directed to our product candidates and/or technologies may not be considered patentable by the USPTO or by patent offices in foreign countries. The USPTO may determine that our patents or patent applications are invalid for obviousness. Such patent applications may not issue as granted patents. One aspect of the determination of patentability of our inventions depends on the scope and content of the “prior art,” information that was or is deemed available to a person of skill in the relevant art prior to the priority date of the claimed invention. There may be prior art of which we are not aware that may affect the patentability of our patent claims or, if issued, affect the validity or enforceability of a patent claim. Even if the patents do issue based on our patent applications, third parties may challenge the validity, enforceability or scope thereof, which may result in such patents being narrowed, invalidated or held unenforceable. Furthermore, even if they are unchallenged, patents in our portfolio may not adequately exclude third parties from practicing relevant technology or prevent others from designing around our claims. If the breadth or strength of our intellectual property position with respect to our product candidates is threatened, it could dissuade companies from collaborating with us to develop and threaten our ability to commercialize our product candidates. In the event of litigation or administrative proceedings, the claims in our issued patents may not be considered valid by courts in the United States or foreign countries.

Intellectual property rights do not necessarily address all potential threats to our competitive advantage.

The degree of future protection afforded by our intellectual property rights is uncertain because intellectual property rights have limitations and may not adequately protect our business or permit us to maintain our competitive advantage. For example:

- others may be able to make product candidates that are similar to ours but that are not covered by the claims of the patents that we own or have exclusively licensed by designing around features of our product candidates;
- we or our licensors or future collaborators might not have been the first to make the inventions covered by the issued patent or pending patent application that we own or have exclusively licensed;
- we or our licensors or future collaborators might not have been the first to file patent applications covering certain of our inventions;
- others may independently develop similar or alternative technologies or duplicate any of our technologies without infringing our intellectual property rights;

- it is possible that noncompliance with the USPTO and foreign governmental patent agencies requirement for a number of procedural, documentary, fee payment and other provisions during the patent process can result in abandonment or lapse of a patent or patent application, and partial or complete loss of patent rights in the relevant jurisdiction;
- it is possible that our pending patent applications will not lead to issued patents;
- issued patents that we own or have exclusively licensed may be revoked, modified, or held invalid or unenforceable, as a result of legal challenges by our competitors;
- our competitors might conduct research and development activities in countries where we do not have patent rights and then use the information learned from such activities to develop competitive products for sale in our major commercial markets;
- we may not develop additional proprietary technologies that are patentable;
- we cannot predict the scope of protection of any patent issuing based on our patent applications, including whether the patent applications that we own or in-license will result in issued patents with claims that directed to our product candidates or uses thereof in the United States or in other foreign countries;
- there may be significant pressure on the U.S. government and international governmental bodies to limit the scope of patent protection both inside and outside the United States for disease treatments that prove successful, as a matter of public policy regarding worldwide health concerns;
- countries other than the United States may have patent laws less favorable to patentees than those upheld by U.S. courts, allowing foreign competitors a better opportunity to create, develop and market competing product candidates;
- the claims of any patent issuing based on our patent applications may not provide protection against competitors or any competitive advantages, or may be challenged by third parties;
- if enforced, a court may not hold that our patents are valid, enforceable and infringed;
- we may need to initiate litigation or administrative proceedings to enforce and/or defend our patent rights which will be costly whether we win or lose;
- we may choose not to file a patent application in order to maintain certain trade secrets or know-how, and a third party may subsequently file a patent application covering such intellectual property;
- we may fail to adequately protect and police our trademarks and trade secrets; and
- the patents of others may have an adverse effect on our business, including if others obtain patents claiming subject matter similar to or improving that covered by our patents and patent applications.

Should any of these or similar events occur, they could significantly harm our business, results of operations and prospects.

We may not identify relevant third-party patents or may incorrectly interpret the relevance, scope or expiration of a third-party patent, which might adversely affect our ability to develop and market our products.

Our patent searches or analyses, including the identification of relevant patents, the scope of patent claims or the expiration of relevant patents, may not have been complete or thorough, and we may not have identified each and every third-party patent and pending application in the United States and abroad that is relevant to or necessary for the commercialization of our product candidates in any jurisdiction.

The scope of a patent claim is determined by an interpretation of the law, the written disclosure in a patent and the patent's prosecution history. Our interpretation of the relevance or the scope of a patent or a pending application may be incorrect. For example, we may incorrectly determine that our products are not covered by a third-party patent or may incorrectly predict whether a third-party's pending application will issue with claims of relevant scope. Our determination of the expiration date of any patent in the United States or abroad that we consider

relevant may be incorrect. Our failure to identify and correctly interpret relevant patents may negatively impact our ability to develop and market our products.

We are currently party to an in-license agreement under which we were granted rights to manufacture certain components of our product candidates. If we breach our obligations under these agreements, we may be required to pay damages, lose our rights to these technologies or both, which would adversely affect our business and prospects.

We rely, in part, on license and other strategic agreements, which subject us to various obligations, including payment obligations for achievement of certain milestones on product sales. For example, with respect to our ReCODE platform, we have an exclusive license to a patent portfolio containing three families of United States and foreign patents and patent applications co-owned by TSRI and The Regents of the University of California. If we fail to comply with the obligations under our license agreements, including as a result of COVID-19 impacting our operations, or use the intellectual property licensed to us in an unauthorized manner, we may be required to pay damages and our licensors may have the right to terminate the license. If our license agreements are terminated, we may experience significant delays, difficulties, and costs in developing new cell lines and identifying an alternative source to manufacture components of our candidate products covered by our agreements and those being tested or approved in combination with such products. Such an occurrence could materially adversely affect the value of the product candidates being developed under any such agreement.

In addition, the agreements under which we license intellectual property or technology to or from third parties are complex, and certain provisions in such agreements may be susceptible to multiple interpretations. The resolution of any contract interpretation disagreement that may arise could narrow what we believe to be the scope of our rights to the relevant intellectual property or technology or increase what we believe to be our financial or other obligations under the relevant agreement, either of which could have a material adverse effect on our business, financial condition, results of operations and prospects.

We control the prosecution of patents resulting from licensed technology. In the event we breach any of our obligations related to such prosecution, we may incur significant liability to our licensing partners.

Licensing of intellectual property involves complex legal, business and scientific issues and is complicated by the rapid pace of scientific discovery in our industry. Disputes may arise regarding intellectual property subject to a licensing agreement, including:

- the scope of rights granted under the license agreement and other interpretation-related issues;
- the extent to which our technology and processes infringe on intellectual property of the licensor that is not subject to the licensing agreement;
- the sublicensing of patent and other rights;
- our diligence obligations under the license agreement and what activities satisfy those diligence obligations;
- the ownership of inventions and know-how resulting from the creation or use of intellectual property by us alone or with our licensors and partners;
- the scope and duration of our payment obligations; and
- the priority of invention of patented technology.

If disputes over intellectual property and other rights that we have licensed prevent or impair our ability to maintain our current licensing arrangements on acceptable terms, we may be unable to successfully develop and commercialize the affected product candidates. We are generally also subject to all of the same risks with respect to protection of intellectual property that we license as we are for intellectual property that we own, which are described herein. If we or our licensor fail to adequately protect this intellectual property, our ability to develop, manufacture, or commercialize products could suffer.

In addition, while we cannot currently determine the amount of the royalty obligations we would be required to pay on sales of future products, if any, the amounts may be significant. The amount of our future royalty obligations will depend on the technology and intellectual property we use in products that we successfully develop and commercialize, if any. Therefore, even if we successfully develop and commercialize products, we may be unable to achieve or maintain profitability.

If we are unable to successfully obtain rights to required third-party intellectual property rights or maintain the existing intellectual property rights we have, we may have to abandon development of the relevant research programs or product candidates and our business, financial condition, results of operations and prospects could suffer.

In the future, we may need to obtain additional licenses of third-party technology that may not be available to us or are available only on commercially unreasonable terms, and which may cause us to operate our business in a more costly or otherwise adverse manner that was not anticipated.

We currently own intellectual property directed to our product candidates and other proprietary technologies. Other pharmaceutical companies and academic institutions may also have filed or are planning to file patent applications potentially relevant to our business. From time to time, in order to avoid infringing these third-party patents, we may be required to license technology from additional third parties to further develop or commercialize our product candidates. Should we be required to obtain licenses to any third-party technology, including any such patents required to manufacture, use or sell our product candidates, such licenses may not be available to us on commercially reasonable terms, or at all. The inability to obtain any third-party license required to develop or commercialize any of our product candidates could cause us to abandon any related efforts, which could seriously harm our business and operations.

The licensing or acquisition of third-party intellectual property rights is a competitive area, and several more established companies may pursue strategies to license or acquire third-party intellectual property rights we may consider attractive or necessary. These established companies may have a competitive advantage over us due to their size, capital resources and greater clinical development and commercialization capabilities. In addition, companies that perceive us to be a competitor may be unwilling to assign or license rights to us.

Moreover, some of our owned and in-licensed patents or patent applications or future patents are or may be co-owned with third parties. If we are unable to obtain an exclusive license to any such third-party co-owners' interest in such patents or patent applications, such co-owners may be able to license their rights to other third parties, including our competitors, and our competitors could market competing products and technology. In addition, we may need the cooperation of any such co-owners of our patents in order to enforce such patents against third parties, and such cooperation may not be provided to us. Furthermore, our owned and in-licensed patents may be subject to a reservation of rights by one or more third parties. Any of the foregoing could have a material adverse effect on our competitive position, business, financial conditions, results of operations and prospects.

If we are sued for infringing intellectual property rights of third parties, such litigation could be costly and time consuming and could prevent or delay us from developing or commercializing our product candidates.

Our commercial success depends, in part, on our ability to develop, manufacture, market and sell our product candidates without infringing the intellectual property and other proprietary rights of third parties. Third parties may allege that we have infringed or misappropriated their intellectual property. Litigation or other legal proceedings relating to intellectual property claims, with or without merit, is unpredictable and generally expensive and time consuming and, even if resolved in our favor, is likely to divert significant resources from our core business, including distracting our technical and management personnel from their normal responsibilities. In addition, there could be public announcements of the results of hearings, motions or other interim proceedings or developments and if securities analysts or investors perceive these results to be negative, it could have a substantial adverse effect on the trading price of our ADSs. Such litigation or proceedings could substantially increase our operating losses and reduce the resources available for development activities or any future sales, marketing or distribution activities. We may not have sufficient financial or other resources to adequately conduct such litigation or proceedings. Some of our competitors may be able to sustain the costs of such litigation or proceedings more effectively than we can.

because of their greater financial resources and more mature and developed intellectual property portfolios. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could have a material adverse effect on our ability to compete in the marketplace.

There is a substantial amount of intellectual property litigation in the biotechnology and pharmaceutical industries, and we may become party to, or threatened with, litigation or other adversarial proceedings regarding intellectual property rights with respect to our product candidates. We may develop product candidates and other proprietary technologies that infringe existing or future patents owned by third parties. Third parties may assert infringement claims against us based on existing or future intellectual property rights. We believe that the relevant claims of these third party patents are likely invalid or unenforceable, and we may choose to challenge those patents, though the outcome of any challenge that we may initiate in the future is uncertain. We may also decide in the future to seek a license to those third party patents, but we might not be able to do so on reasonable terms. Proving invalidity may be difficult. For example, in the United States, proving invalidity in court requires a showing of clear and convincing evidence to overcome the presumption of validity enjoyed by issued patents. If we are found to infringe a third party's intellectual property rights, we could be forced, including by court order, to cease developing, manufacturing or commercializing the infringing candidate product or product. Alternatively, we may be required to obtain a license from such third party in order to use the infringing technology and continue developing, manufacturing or marketing the infringing candidate product or product. However, we may not be able to obtain any required license on commercially reasonable terms or at all. Even if we were able to obtain a license, it could be non-exclusive, thereby giving our competitors access to the same technologies licensed to us. In addition, we could be found liable for monetary damages, including treble damages and attorneys' fees if we are found to have willfully infringed a patent. A finding of infringement could prevent us from commercializing our investigational products or force us to cease some of our business operations, which could materially harm our business.

We may not be aware of patents that have already been issued and that a third party, for example, a competitor in the fields in which we are developing our product candidates, might assert are infringed by our current or future product candidates, including claims to compositions, formulations, methods of manufacture or methods of use or treatment that cover our product candidates. It is also possible that patents owned by third parties of which we are aware, but which we do not believe are relevant to our product candidates and other proprietary technologies we may develop, could be found to be infringed by our product candidate. In addition, because patent applications can take many years to issue, there may be currently pending patent applications that may later result in issued patents that our product candidates may infringe. Our competitors in both the United States and abroad, many of which have substantially greater resources and have made substantial investments in patent portfolios and competing technologies, may have applied for or obtained or may in the future apply for and obtain, patents that will prevent, limit or otherwise interfere with our ability to make, use and sell our product candidates. The pharmaceutical and biotechnology industries have produced a considerable number of patents, and it may not always be clear to industry participants, including us, which patents cover various types of products or methods of use. The coverage of patents is subject to interpretation by the courts, and the interpretation is not always uniform. If we were sued for patent infringement, we would need to demonstrate that our product candidates, products or methods either do not infringe the patent claims of the relevant patent or that the patent claims are invalid or unenforceable, and we may not be able to do this. Proving invalidity may be difficult. For example, in the United States, proving invalidity in court requires a showing of clear and convincing evidence to overcome the presumption of validity enjoyed by issued patents, and a court of competent jurisdiction may not invalidate the claims of any such U.S. patent. Even if we are successful in these proceedings, we may incur substantial costs and the time and attention of our management and scientific personnel could be diverted in pursuing these proceedings, which could have a material adverse effect on our business and operations. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during litigation. In addition, we may not have sufficient resources to bring these actions to a successful conclusion.

We may choose to challenge the enforceability or validity of claims in a third party's U.S. patent by requesting that the USPTO review the patent claims in an *ex-parte* re-exam, IPR or post-grant review proceedings. These proceedings are expensive and may consume our time or other resources. We may choose to challenge a third party's patent in patent opposition proceedings in the EPO, or other foreign patent office. The costs of these opposition proceedings could be substantial and may consume our time or other resources. If we fail to obtain a

favorable result at the USPTO, EPO or other patent office then we may be exposed to litigation by a third party alleging that the patent may be infringed by our product candidates or proprietary technologies.

If we are found to infringe a third-party's intellectual property rights, we could be forced, including by court order, to cease developing, manufacturing or commercializing the infringing product candidate or product. Alternatively, we may be required to obtain a license from such third-party in order to use the infringing technology and continue developing, manufacturing or marketing the infringing product candidate. However, we may not be able to obtain any required license on commercially reasonable terms or at all. Even if we were able to obtain a license, it could be non-exclusive, thereby giving our competitors access to the same technologies licensed to us. In addition, we could be found liable for monetary damages, including treble damages and attorneys' fees if we are found to have willfully infringed a patent. A finding of infringement could prevent us from commercializing our product candidates or force us to cease some of our business operations and could divert the time and attention of our technical personnel and management, cause development delays, and/or require us to develop non-infringing technology, which may not be possible on a cost-effective basis, any of which could materially harm our business. In the event of a successful claim of infringement against us, we may have to pay substantial monetary damages, including treble damages and attorneys' fees for willful infringement, pay royalties and other fees, redesign our infringing drug or obtain one or more licenses from third parties, which may be impossible or require substantial time and monetary expenditure. Claims that we have misappropriated the confidential information or trade secrets of third parties could have a similar negative impact on our business.

We may become involved in lawsuits to protect or enforce our patents or other intellectual property, which could be expensive, time consuming and unsuccessful.

Competitors or other third parties may infringe our patents, trademarks or other intellectual property. To counter infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time consuming and divert the time and attention of our management and scientific personnel. Our pending patent applications cannot be enforced against third parties practicing the technology claimed in such applications unless and until a patent issues from such applications. Any claims we assert against perceived infringers could provoke these parties to assert counterclaims against us alleging that we infringe their patents, in addition to counterclaims asserting that our patents are invalid or unenforceable, or both. In patent litigation in the United States, defendant counterclaims alleging invalidity and/or unenforceability are commonplace. Grounds for a validity challenge could be an alleged failure to meet any of several statutory requirements, including lack of novelty, obviousness, non-enablement or insufficient written description. Grounds for an unenforceability assertion could be an allegation that someone connected with prosecution of the patent withheld relevant information from the USPTO or made a misleading statement during prosecution. The outcome following legal assertions of invalidity and unenforceability is unpredictable. In any patent infringement proceeding, there is a risk that a court will decide that a patent of ours is invalid or unenforceable, in whole or in part, and that we do not have the right to stop the other party from using the invention at issue. There is also a risk that, even if the validity of such patents is upheld, the court will construe the patent's claims narrowly or decide that we do not have the right to stop the other party from using the invention at issue on the grounds that our patent claims do not cover the invention, or decide that the other party's use of our patented technology falls under the safe harbor to patent infringement under 35 U.S.C. §271(e)(1). An adverse outcome in a litigation or proceeding involving our patents could limit our ability to assert our patents against those parties or other competitors and may curtail or preclude our ability to exclude third parties from making and selling similar or competitive products. Any of these occurrences could adversely affect our competitive business position, business prospects and financial condition. Similarly, if we assert trademark infringement claims, a court may determine that the marks we have asserted are invalid or unenforceable, or that the party against whom we have asserted trademark infringement has superior rights to the marks in question. In this case, we could ultimately be forced to cease use of such trademarks.

Even if we establish infringement, the court may decide not to grant an injunction against further infringing activity and instead award only monetary damages, which may or may not be an adequate remedy. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during litigation. There could also be public announcements of the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, it could have a material adverse effect on the trading price of our ADSs. Moreover, we may not have sufficient financial or other resources to file and pursue such

infringement claims, which typically last for years before they are concluded. Even if we ultimately prevail in such claims, the monetary cost of such litigation and the diversion of the attention of our management and scientific personnel could outweigh any benefit we receive as a result of the proceedings.

Because of the expense and uncertainty of litigation, we may not be in a position to enforce our intellectual property rights against third parties.

Because of the expense and uncertainty of litigation, we may conclude that even if a third-party is infringing our issued patent, any patents that may be issued as a result of our pending or future patent applications or other intellectual property rights, the risk-adjusted cost of bringing and enforcing such a claim or action may be too high or not in the best interest of our company or our shareholders, or it may be otherwise impractical or undesirable to enforce our intellectual property against some third parties. Our competitors or other third parties may be able to sustain the costs of complex patent litigation or proceedings more effectively than we can because of their greater financial resources and more mature and developed intellectual property portfolios. In such cases, we may decide that the more prudent course of action is to simply monitor the situation or initiate or seek some other non-litigious action or solution. In addition, the uncertainties associated with litigation could compromise our ability to raise the funds necessary to continue our clinical trials, continue our internal research programs, in-license needed technology or other product candidates or enter into development partnerships that would help us bring our product candidates to market.

Further, proceedings to enforce our patent rights in foreign jurisdictions could result in substantial costs and divert our efforts and attention from other aspects of our business, could put our patents at risk of being invalidated or interpreted narrowly and our patent applications at risk of not issuing and could provoke third parties to assert claims against us. We may not prevail in any such lawsuits that we initiate and the damages and other remedies awarded, if any, may not be commercially meaningful.

We may be subject to claims that we have wrongfully hired an employee from a competitor or that our employees, consultants or independent contractors have wrongfully used or disclosed confidential information of third parties.

As is common in the pharmaceutical industry, in addition to our employees, we engage the services of consultants to assist us in the development of our product candidates. Many of these consultants, and many of our employees, were previously employed at, or may have previously provided or may be currently providing consulting services to, other pharmaceutical companies including our competitors or potential competitors. We could in the future be subject to claims that we or our employees have inadvertently or otherwise used or disclosed alleged trade secrets or other confidential information of former employers or competitors. Although we try to ensure that our employees and consultants do not use the intellectual property, proprietary information, know-how or trade secrets of others in their work for us, we may become subject to claims that we caused an employee to breach the terms of his or her non-competition or non-solicitation agreement, or that we or these individuals have, inadvertently or otherwise, used or disclosed the alleged trade secrets or other proprietary information of a former employer or competitor.

While we may litigate to defend ourselves against these claims, even if we are successful, litigation could result in substantial costs and could be a distraction to management. If our defenses to these claims fail, in addition to requiring us to pay monetary damages, a court could prohibit us from using technologies or features that are essential to our product candidates, if such technologies or features are found to incorporate or be derived from the trade secrets or other proprietary information of the former employers. Moreover, any such litigation or the threat thereof may adversely affect our reputation, our ability to form strategic alliances or sublicense our rights to collaborators, engage with scientific advisors or hire employees or consultants, each of which would have an adverse effect on our business, results of operations and financial condition. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management.

Changes in patent law in the United States and other jurisdictions could diminish the value of patents in general, thereby impairing our ability to protect our intellectual property rights throughout the world.

As is the case with other biologics companies, our success is heavily dependent on intellectual property, particularly patents. Obtaining and enforcing patents in the biologics industry involves both technological and legal complexity and is therefore costly, time consuming and inherently uncertain. Changes in either the patent laws or interpretation of the patent laws in the United States could increase the uncertainties and costs, and may diminish our ability to protect our inventions, obtain, maintain, and enforce our intellectual property rights and, more generally, could affect the value of our intellectual property or narrow the scope of our owned and licensed patents.

Patent protection is available on a national or regional level. Filing, prosecuting and defending patents throughout the world and on all of our product candidates would be prohibitively expensive. As such, our intellectual property rights outside the United States may not extend to all other possible countries outside the United States and we may not be able to prevent third parties from practicing our inventions in countries outside the United States where we do not have patent protection, or from selling in and importing products into other jurisdictions made using our inventions in such countries outside the United States. Competitors may use our technologies in jurisdictions where we have not obtained patent protection to develop their own products or technology and may export otherwise infringing products or technology to territories where we have patent protection, but enforcement rights are not as strong as those in the United States. These products may compete with our products, and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing. Further, the legal systems of certain countries, particularly certain developing countries, do not favor the enforcement of patents and other intellectual property protection, particularly those relating to pharmaceuticals or biologics, which could make it difficult for us to stop the infringement of our patents or marketing of competing products in violation of our proprietary rights generally. In addition, certain developing countries, including India, have compulsory licensing laws under which a patent owner may be compelled under certain circumstances to grant licenses to third parties at nominal or no consideration. In those countries, we and our licensors may have limited remedies if patents are infringed or if we or our licensors are compelled to grant a license to a third-party, which could materially diminish the value of those patents. In addition, many countries limit the enforceability of patents against government agencies or government contractors. This could limit our potential revenue opportunities. Accordingly, our efforts to enforce our intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop or license.

No earlier than June 1, 2023, European applications will soon have the option, upon grant of a patent, of becoming a Unitary Patent which will be subject to the jurisdiction of the Unitary Patent Court, or UPC. This will be a significant change in European patent practice. As the UPC is a new court system, there is no precedent for the court, increasing the uncertainty of any litigation.

Patent reform legislation in the United States and other countries, including the Leahy-Smith America Invents Act, the Leahy-Smith Act, signed into law on September 16, 2011, could increase those uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents. The Leahy-Smith Act includes a number of significant changes to U.S. patent law. These include provisions that affect the way patent applications are prosecuted, redefine prior art and provide more efficient and cost-effective avenues for competitors to challenge the validity of patents. These include allowing third-party submission of prior art to the USPTO during patent prosecution and additional procedures to attack the validity of a patent by USPTO administered post-grant proceedings, including post-grant review, IPR, and derivation proceedings. Further, because of a lower evidentiary standard in these USPTO post-grant proceedings compared to the evidentiary standard in U.S. federal courts necessary to invalidate a patent claim, a third party could potentially provide evidence in a USPTO proceeding sufficient for the USPTO to hold a claim invalid even though the same evidence would be insufficient to invalidate the claim if first presented in a district court action. Accordingly, a third party may attempt to use the USPTO procedures to invalidate our patent claims that would not have been invalidated if first challenged by the third party as a defendant in a district court action. Thus, the Leahy-Smith Act and its implementation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents, all of which could have a material adverse effect on our business, financial condition, results of operations and prospects.

After March 2013, under the Leahy-Smith Act, the United States transitioned to a first inventor to file system in which, assuming that the other statutory requirements are met, the first inventor to file a patent application will be entitled to the patent on an invention regardless of whether a third-party was the first to invent the claimed invention. A third party that files a patent application in the USPTO after March 2013, but before we file an application covering the same invention, could therefore be awarded a patent covering an invention of ours even if we had made the invention before it was made by such third party. This will require us to be cognizant going forward of the time from invention to filing of a patent application. Since patent applications in the United States and most other countries are confidential for a period of time after filing or until issuance, we or our licensors may not be the first to either (i) file any patent application related to our product candidates and other proprietary technologies we may develop or (ii) invent any of the inventions claimed in our or our licensor's patents or patent applications. Even where we have a valid and enforceable patent, we may not be able to exclude others from practicing the claimed invention where the other party can show that they used the invention in commerce before our filing date or the other party benefits from a compulsory license. However, the Leahy-Smith Act and its implementation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents, all of which could have a material adverse effect on our business, financial condition, results of operations and prospects.

In addition, the patent positions of companies in the development and commercialization of pharmaceuticals are particularly uncertain. The U.S. Supreme Court has ruled on several patent cases in recent years, either narrowing the scope of patent protection available in certain circumstances or weakening the rights of patent owners in certain situations. Depending on future actions by the U.S. Congress, the U.S. courts, the USPTO and the relevant law-making bodies in other countries, the laws and regulations governing patents could change in unpredictable ways that would weaken our ability to obtain new patents or to enforce our existing patents and patents that we might obtain in the future. For example, in the 2013 case *Assoc. for Molecular Pathology v. Myriad Genetics, Inc.*, the U.S. Supreme Court held that certain claims to DNA molecules are not patentable. While we do not believe that any of the patents owned or licensed by us will be found invalid based on this decision, future decisions by the courts, the U.S. Congress or the USPTO may impact the value of our patents.

Obtaining and maintaining patent protection depends on compliance with various procedural, document submissions, fee payment and other requirements imposed by governmental patent agencies, and our patent protection could be reduced or eliminated for non-compliance with these requirements.

Periodic maintenance fees, renewal fees, annuities fees and various other governmental fees on patents and/or patent applications are due to be paid to the USPTO and foreign patent agencies in several stages over the lifetime of the patent and/or patent application. The USPTO and various foreign governmental patent agencies also require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent application process. While an inadvertent lapse, including due to the effect of the COVID-19 pandemic on us or our patent maintenance vendors, can in many cases be cured by payment of a late fee or by other means in accordance with the applicable rules, there are situations in which noncompliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. Non-compliance events that could result in abandonment or lapse of a patent or patent application include, but are not limited to, failure to respond to official actions within prescribed time limits, non-payment of fees and failure to properly legalize and submit formal documents. If we fail to maintain the patents and patent applications covering our product candidates, our competitive position would be adversely affected.

We may rely on trade secret and proprietary know-how which can be difficult to trace and enforce and, if we are unable to protect the confidentiality of our trade secrets, our business and competitive position would be harmed.

In addition to seeking patents for some of our technology and product candidates, we may also rely on trade secrets, including unpatented know-how, technology and other proprietary information, to maintain our competitive position. Elements of our product candidate, including processes for their preparation and manufacture, may involve proprietary know-how, information, or technology that is not covered by patents, and thus for these aspects we may consider trade secrets and know-how to be our primary intellectual property. Any disclosure, either intentional or unintentional, by our employees, the employees of third parties with whom we share our facilities or third-party consultants and vendors that we engage to perform research, clinical trials or manufacturing activities, or misappropriation by third parties (such as through a cybersecurity breach) of our trade secrets or proprietary

information could enable competitors to duplicate or surpass our technological achievements, thus eroding our competitive position in our market. Because we expect to rely on third parties in the development and manufacture of our product candidates, we must, at times, share trade secrets with them. Our reliance on third parties requires us to share our trade secrets, which increases the possibility that a competitor will discover them or that our trade secrets will be misappropriated or disclosed.

Trade secrets and know-how can be difficult to protect. We require our employees to enter into written employment agreements containing provisions of confidentiality and obligations to assign to us any inventions generated in the course of their employment. We and any third parties with whom we share facilities enter into written agreements that include confidentiality and intellectual property obligations to protect each party's property, potential trade secrets, proprietary know-how, and information. We further seek to protect our potential trade secrets, proprietary know-how, and information in part, by entering into non-disclosure and confidentiality agreements with parties who are given access to them, such as our corporate collaborators, outside scientific collaborators, contract research organizations, contract manufacturers, consultants, advisors and other third parties. With our consultants, contractors, and outside scientific collaborators, these agreements typically include invention assignment obligations. We may not have entered into such agreements with each party that may have or has had access to our trade secrets or proprietary technology and processes. Our trade secrets and other confidential proprietary information may be disclosed, or competitors may otherwise gain access to our trade secrets or independently develop substantially equivalent information and techniques. Despite these efforts, any of these parties may breach the agreements and disclose our proprietary information, including our trade secrets, and we may not be able to obtain adequate remedies for such breaches. Enforcing a claim that a party illegally disclosed or misappropriated a trade secret is difficult, expensive and time-consuming, and the outcome is unpredictable. In addition, some courts inside and outside the United States are less willing or unwilling to protect trade secrets. We currently have and may in the future enter into more contract research and manufacturing relationships with organizations that operate in certain countries that are at heightened risk of theft of technology, data and intellectual property, including through direct intrusion by private parties or foreign actors, and those affiliated with or controlled by state actors. If our trade secrets are disclosed in a foreign jurisdiction, competitors worldwide could have access to our proprietary information, and we may be without satisfactory recourse. Such disclosure could have a material adverse effect on our business. Moreover, our ability to protect and enforce our intellectual property rights may be adversely affected by unforeseen changes in foreign intellectual property laws. Further, if any of our trade secrets were to be lawfully obtained or independently developed by a competitor or other third-party, we would have no right to prevent them from using that technology or information to compete with us. If any of our trade secrets were to be disclosed to or independently developed by a competitor or other third-party, our competitive position would be harmed.

We may become subject to claims challenging the inventorship or ownership of our patents and other intellectual property.

We may be subject to claims that former employees, collaborators or other third parties have an interest in our patents or other intellectual property as an inventor or co-inventor. The failure to name the proper inventors on a patent application can result in the patents issuing thereon being unenforceable. Inventorship disputes may arise from conflicting views regarding the contributions of different individuals named as inventors, the effects of foreign laws where foreign nationals are involved in the development of the subject matter of the patent, conflicting obligations of third parties involved in developing our product candidates or as a result of questions regarding co-ownership of potential joint inventions. Litigation may be necessary to resolve these and other claims challenging inventorship and/or ownership. Alternatively, or additionally, we may enter into agreements to clarify the scope of our rights in such intellectual property. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights, such as exclusive ownership of, or right to use, valuable intellectual property. Such an outcome could have a material adverse effect on our business. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management and other employees.

Our licensors may have relied on third-party consultants or collaborators or on funds from third parties, such as the U.S. government, such that our licensors are not the sole and exclusive owners of the patents we in-licensed. If other third parties have ownership rights or other rights to our in-licensed patents, they may be able to license such patents to our competitors, and our competitors could market competing products and technology. This could have a

material adverse effect on our competitive position, business, financial conditions, results of operations, and prospects.

In addition, while it is our policy to require our employees and contractors who may be involved in the conception or development of intellectual property to execute agreements assigning such intellectual property to us, we may be unsuccessful in executing such an agreement with each party who, in fact, conceives or develops intellectual property that we regard as our own. The assignment of intellectual property rights may not be self-executing, or the assignment agreements may be breached, and we may be forced to bring claims against third parties, or defend claims that they may bring against us, to determine the ownership of what we regard as our intellectual property. Such claims could have a material adverse effect on our business, financial condition, results of operations, and prospects.

Patent terms may be inadequate to protect our competitive position on our product candidates for an adequate amount of time.

Patent rights are of limited duration. In the United States, if all maintenance fees are paid timely, the natural expiration of a patent is generally 20 years after its first effective filing date. Given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such candidates might expire before or shortly after such product candidates are commercialized. Even if patents covering our product candidates are obtained, once the patent life has expired for a product, we may be open to competition from biosimilar or generic products. As a result, our patent portfolio may not provide us with sufficient rights to exclude others from commercializing product candidates similar or identical to ours. Upon issuance in the United States, the term of a patent can be increased by patent term adjustment, which is based on certain delays caused by the USPTO, but this increase can be reduced or eliminated based on certain delays caused by the patent applicant during patent prosecution. The term of a U.S. patent may also be shortened if the patent is terminally disclaimed over an earlier-filed patent. A patent term extension, or PTE, based on regulatory delay may be available in the United States. However, only a single patent can be extended for each marketing approval, and any patent can be extended only once, for a single product. Moreover, the scope of protection during the period of the PTE does not extend to the full scope of the claim, but instead only to the scope of the product as approved. Laws governing analogous PTEs in foreign jurisdictions vary widely, as do laws governing the ability to obtain multiple patents from a single patent family. Additionally, we may not receive an extension if we fail to exercise due diligence during the testing phase or regulatory review process, apply within applicable deadlines, fail to apply prior to expiration of relevant patents or otherwise fail to satisfy applicable requirements. Furthermore, our patents covering certain components of our product candidates may expire prior to the commercialization of our product candidates or soon thereafter. As a result, third parties may be able to utilize these components of our products after expiration of these patents. For example, our initial non-natural pAF amino acid patent estate expires in 2025. However, our subsequent patent families, which cover our product candidates as ADCs or IOCs, and which also incorporate the non-natural pAF amino acid, expire between 2032 and 2039.

If we are unable to obtain PTE or restoration, or the term of any such extension is less than we request, the period during which we will have the right to exclusively market our product will be shortened and our competitors may obtain approval of competing products following our patent expiration and may take advantage of our investment in development and clinical trials by referencing our clinical and preclinical data to launch their product earlier than might otherwise be the case, and our revenue could be reduced, possibly materially.

If our trademarks and trade names are not adequately protected, then we may not be able to build name recognition in our markets of interest and our business may be adversely affected.

Our current or future trademarks or trade names may be challenged, infringed, circumvented or declared generic or descriptive or determined to be infringing on other marks. We may not be able to protect our rights to these trademarks and trade names or may be forced to stop using these names, which we need for name recognition by potential partners or customers in our markets of interest. During trademark registration proceedings, we may receive rejections of our applications by the USPTO or in other foreign jurisdictions. Although we would be given an opportunity to respond to those rejections, we may be unable to overcome such rejections. In addition, in the USPTO and in comparable agencies in many foreign jurisdictions, third parties are given an opportunity to oppose pending trademark applications and to seek to cancel registered trademarks. Opposition or cancellation proceedings

may be filed against our trademarks, and our trademarks may not survive such proceedings. If we are unable to establish name recognition based on our trademarks and trade names, we may not be able to compete effectively and our business may be adversely affected. We may license our trademarks and trade names to third parties, such as distributors. Although these license agreements may provide guidelines for how our trademarks and trade names may be used, a breach of these agreements or misuse of our trademarks and trade names by our licensees may jeopardize our rights in or diminish the goodwill associated with our trademarks and trade names.

Moreover, any name we have proposed to use with our product candidate in the United States must be approved by the FDA, regardless of whether we have registered it, or applied to register it, as a trademark. Similar requirements exist in Europe. The FDA typically conducts a review of proposed product names, including an evaluation of potential for confusion with other product names. If the FDA (or an equivalent administrative body in a foreign jurisdiction) objects to any of our proposed proprietary product names, it may be required to expend significant additional resources in an effort to identify a suitable substitute name that would qualify under applicable trademark laws, not infringe the existing rights of third parties and be acceptable to the FDA. Furthermore, in many countries, owning and maintaining a trademark registration may not provide an adequate defense against a subsequent infringement claim asserted by the owner of a senior trademark. At times, competitors or other third parties may adopt trade names or trademarks similar to ours, thereby impeding our ability to build brand identity and possibly leading to market confusion. In addition, there could be potential trade name or trademark infringement claims brought by owners of other registered trademarks or trademarks that incorporate variations of our registered or unregistered trademarks or trade names. If we assert trademark infringement claims, a court may determine that the marks we have asserted are invalid or unenforceable, or that the party against whom we have asserted trademark infringement has superior rights to the marks in question. In this case, we could ultimately be forced to cease use of such trademarks.

Risks Related to Our Securities and Our Status as a Public Company

As of January 1, 2023, we are required to report as a United States domestic issuer and the benefits of a “foreign private issuer” are no longer available to us, which will likely result in additional costs and expenses for us.

As of January 1, 2023, we lost our status as a “foreign private issuer” and are required to adjust our disclosure and reporting to comply with the requirements for domestic U.S. companies. As a result:

- we are required to report on forms that are applicable to U.S. companies, such as Forms 10-K, 10-Q and 8-K, rather than the forms formerly used by us, such as Forms 20-F and 6-K;
- we are required to hold annual meetings of our shareholders and will be required to file a definitive proxy statement that is in compliance with Schedule 14A;
- we can no longer make use of the shelf registration statement on Form F-3 that was declared effective on August 5, 2022;
- if we engage in capital raising activities, there is a higher likelihood that investors may require us to file resale registration statements with the SEC as a condition to any such financing; and
- we may be required to modify certain of our policies to comply with accepted governance practices associated with U.S. domestic issuers.

We expect that complying with these additional requirements would increase our legal and audit fees which in turn, could have a material adverse effect on our business, financial condition and results of operations. In addition, as a result of being considered a “domestic issuer” for reporting and disclosure requirements:

- we are no longer exempt from certain of the provisions of U.S. securities laws such as (i) Regulation FD, which restricts the selective disclosure of material information, (ii) exemptions for filing beneficial ownership reports under Section 16(a) of the Exchange Act for executive officers, directors and 10% shareholders (Forms 3, 4, and 5), and (iii) the Section 16(b) short swing profit rules;
- we are no longer permitted to disclose compensation information for our executive officers on an aggregate rather than an individual basis, although such exemption may still be available to us as long as we remain an “emerging growth company”; and

- we have lost the ability to rely upon exemptions from Nasdaq corporate governance requirements that are available to foreign private issuers.

The trading price of our ADSs may be volatile, and you could lose all or part of your investment.

The trading price of our ADSs has been and will likely continue to be highly volatile and could be subject to wide fluctuations in response to various factors, some of which are beyond our control, including limited trading volume. The stock market in general and the market for biologics companies in particular have experienced extreme volatility that has often been unrelated to the operating performance of particular companies. As a result of this volatility, investors may not be able to sell their ADSs at or above the price paid for the ADSs. In addition to the factors discussed in “*Item 1A. Risk Factors*” and elsewhere in this Annual Report, the factors that could cause significant fluctuations in the trading price of our ADSs include:

- positive or negative results from preclinical studies and clinical trials by us, our collaborators or competitors;
- concerns regarding the safety of our product candidates or ADCs in general;
- the timing of commencing, enrolling and announcing results from clinical trials;
- decisions as to which product candidates, indications or discovery programs we chose to pursue;
- announcements regarding competitive products or technologies or the biologics industry in general;
- actions taken or guidance provided by regulatory agencies with respect to our clinical trials or regulatory submissions;
- changes or developments in laws or regulations applicable to our product candidates and our markets, including in the United States and China;
- changes to our relationships with collaborators, manufacturers or suppliers;
- the loss of any of our key scientific or management personnel;
- changes in the structure of healthcare payment systems;
- actual or anticipated fluctuations in our operating results;
- changes in financial estimates or recommendations by securities analysts;
- potential acquisitions, financing, collaborations or other corporate transactions;
- the loss of rights under license, strategic or other research and development agreements;
- the results of our efforts to discover, develop, acquire or in-license additional product candidates;
- the trading volume of our ADSs on Nasdaq;
- sales of our ADSs or ordinary shares by us, members of our senior management and directors or our significant shareholders or the anticipation that such sales may occur in the future;
- general macroeconomic, geopolitical, and market conditions and overall fluctuations in the financial markets in the United States or China, including due to bank failures, civil or political unrest (such as the ongoing conflict between Ukraine and Russia), terrorism, insurrection or war, man-made or natural disasters;
- stock market price and volume fluctuations of comparable companies and, in particular, those that operate in the biologics industry;
- investors’ general perception of us and our business;
- public health pandemics or epidemics, including the ongoing and future impact of the COVID-19 pandemic and actions taken to slow its spread; and
- other events and factors, many of which are beyond our control.

These and other market and industry factors may cause the market price and demand for our ADSs to fluctuate substantially, regardless of our actual operating performance, which may limit or prevent investors from selling their ADSs at or above the price paid for the ADSs and may otherwise negatively affect the liquidity of our ADSs. The trading prices for common stock of other biologics companies have also been highly volatile as a result of the COVID-19 pandemic and the ongoing conflict between Ukraine and Russia.

Any such negative outcome could result in payments of substantial damages or fines, damage to our reputation or adverse changes to our business practices. Defending against litigation is costly and time consuming, and could divert our management's attention and our resources. Furthermore, during the course of litigation, there could be negative public announcements of the results of hearings, motions or other interim proceedings or developments, which could have a negative effect on the market price of our ADSs.

Holders of our ADSs have fewer rights than our shareholders and must act through the depositary to exercise their rights.

Holders of our ADSs do not have the same rights as our shareholders and may only exercise their voting rights with respect to the underlying ordinary shares in accordance with the provisions of the deposit agreement. Holders of the ADSs must appoint the depositary or its nominee as their representative to exercise the voting rights attaching to the ordinary shares represented by the ADSs. When a general meeting is convened, if you hold ADSs, you may not receive sufficient notice of a shareholders' meeting to permit you to withdraw the ordinary shares underlying your ADSs to allow you to vote with respect to any specific matter. We will take all commercially reasonable efforts to cause the depositary to extend voting rights to you in a timely manner, but you may not receive voting materials in time to instruct the depositary to vote, and it is possible that you, or persons who hold their ADSs through brokers, dealers or other third parties, will not have the opportunity to exercise a right to vote. Furthermore, the depositary will not be liable for any failure to carry out any instructions to vote, for the manner in which any vote is cast or for the effect of any such vote. As a result, you may not be able to exercise your right to vote and you may lack recourse if your ADSs are not voted as you request. In addition, in your capacity as an ADS holder, you will not be able to call a shareholders' meeting.

ADS holders may not be entitled to a jury trial with respect to claims arising under the deposit agreement, which could result in less favorable outcomes to the plaintiff(s) in any such action.

The deposit agreement governing the ADSs representing our ordinary shares provides that holders and beneficial owners of ADSs irrevocably waive the right to a trial by jury in any legal proceeding arising out of or relating to the deposit agreement, our ordinary shares or the ADSs or the transactions contemplated thereby, including claims under federal securities laws, against us or the depositary to the fullest extent permitted by applicable law. If this jury trial waiver provision is prohibited by applicable law, an action could nevertheless proceed under the terms of the deposit agreement with a jury trial. To our knowledge, the enforceability of a jury trial waiver under the federal securities laws has not been finally adjudicated by a federal court. However, we believe that a jury trial waiver provision is generally enforceable under the laws of the State of New York, which govern the deposit agreement, by a court of the State of New York or a federal court in New York, which have non-exclusive jurisdiction (other than for claims brought by holders of our ADSs, which may only be instituted in a state or federal court in New York, New York), over matters arising under the deposit agreement, applying such law. In determining whether to enforce a jury trial waiver provision, New York courts and federal courts will consider whether the visibility of the jury trial waiver provision within the agreement is sufficiently prominent such that a party has knowingly waived any right to trial by jury. We believe that this is the case with respect to the deposit agreement, our ordinary shares and the ADSs and the transactions contemplated thereby. In addition, New York courts will not enforce a jury trial waiver provision in order to bar a viable setoff or counterclaim sounding in fraud or one which is based upon a creditor's negligence in failing to liquidate collateral upon a guarantor's demand, or in the case of an intentional tort claim (as opposed to a contract dispute), none of which we believe are applicable in the case of the deposit agreement, our ordinary shares or the ADSs or the transactions contemplated thereby. No condition, stipulation or provision of the deposit agreement or ADSs serves as a waiver by any holder or beneficial owner of ADSs or by us or the depositary of compliance with any provision of the federal securities laws. If you or any other holder or beneficial owner of ADSs brings a claim against us or the depositary in connection with matters arising under the deposit agreement, our ordinary shares or the ADSs or the transactions contemplated thereby, you or such other holder or beneficial owner may not be entitled to a jury trial with respect to such claims, which may

have the effect of limiting and discouraging lawsuits against us and / or the depositary. If a lawsuit is brought against us and / or the depositary under the deposit agreement, it may be heard only by a judge or justice of the applicable trial court, which would be conducted according to different civil procedures and may augur different results than a trial by jury would have had, including results that could be less favorable to the plaintiff(s) in any such action, depending on, among other things, the nature of the claims, the judge or justice hearing such claims, and the venue of the hearing.

You may not receive distributions on our ordinary shares represented by the ADSs or any value for them if it is illegal or impractical to make them available to holders of ADSs.

Although we do not have any present plans to declare or pay any dividends on our ordinary shares, in the event we declare and pay any dividends, the depositary for the ADSs has agreed to pay to you the cash dividends or other distributions it or the custodian receives on our ordinary shares or other deposited securities after deducting its fees and expenses. You will receive these distributions in proportion to the number of our ordinary shares your ADSs represent. However, in accordance with the limitations set forth in the deposit agreement, it may be unlawful or impractical to make a distribution available to holders of ADSs. We have no obligation to register under United States securities laws any offering of ADSs, ordinary shares or other securities received through such distributions. We also have no obligation to take any other action to permit distribution on the ADSs, ordinary shares, rights or anything else to holders of the ADSs. This means that you may not receive the distributions we make on our ordinary shares or any value from them if it is unlawful or impractical to make them available to you. These restrictions may have an adverse effect on the value of your ADSs.

Your right to participate in any future rights offerings may be limited, which may cause dilution to your holdings.

We may from time to time distribute rights to our shareholders, including rights to acquire our securities. However, we cannot make rights available to you in the United States unless we register the rights and the securities to which the rights relate under the Securities Act or an exemption from the registration requirements is available. Also, under the deposit agreement, the depositary bank will not make rights available to you unless either both the rights and any related securities are registered under the Securities Act, or the distribution of them to ADS holders is exempted from registration under the Securities Act. We are under no obligation to file a registration statement with respect to any such rights or securities or to endeavor to cause such a registration statement to be declared effective. Moreover, we may not be able to establish an exemption from registration under the Securities Act. If the depositary does not distribute the rights, it may, under the deposit agreement, either sell them, if possible, or allow them to lapse. Accordingly, you may be unable to participate in our rights offerings and may experience dilution in your holdings.

Because we do not anticipate paying any cash dividends on our ADSs in the foreseeable future, capital appreciation, if any, will be your sole source of gains and you may never receive a return on your investment.

We have never declared or paid a dividend on our ordinary shares in the past, and we currently intend to retain our future earnings, if any, to fund the development and growth of our business. Therefore, you should not rely on an investment in our ADSs to provide dividend income. Our board of directors has complete discretion as to whether to distribute dividends, subject to certain restrictions under Cayman Islands law, namely that our company may only pay dividends out of profits or out of the credit standing in our share premium account, and provided always that in no circumstances may a dividend be paid if it would result in our inability to pay our debts as they fall due in the ordinary course of business. In addition, our shareholders may, subject to our memorandum and articles of association, by ordinary resolution declare a dividend, but no dividend may exceed the amount recommended by our board of directors. Even if our board of directors decides to declare and pay dividends, the timing, amount and form of future dividends, if any, will depend on, among other things, our future results of operations and cash flow, our capital requirements and surplus, the amount of distributions, if any, received by us from our subsidiaries, our financial condition, contractual restrictions and other factors deemed relevant by our board of directors. As a result, capital appreciation, if any, on our ADSs will be your sole source of gains for the foreseeable future. Investors seeking cash dividends should not purchase our ADSs.

Our ability to utilize our net operating loss carryforwards and certain other tax attributes may be limited.

As of December 31, 2022, we had U.S. federal, state and foreign net operating loss carryforwards of approximately \$103.5 million, \$136.2 million, and \$13.7 million, respectively, which will begin to expire in 2025, 2028 and 2023, respectively, unless previously utilized. Additionally, as of December 31, 2022, we also had U.S. federal and foreign net operating loss carryforwards of approximately \$107.1 million and \$1.7 million, respectively, which can be carried forward indefinitely. As of December 31, 2022, we also had U.S. federal R&D tax credit carryforwards of approximately \$12.3 million which will begin to expire in 2024 unless previously utilized. As of December 31, 2022, the Company had state tax credit carryforwards of approximately \$8.9 million, which can be carried forward indefinitely.

It is possible that some of these net operating losses and other tax attributes may expire prior to our generating sufficient taxable income to use them. Under current law, U.S. federal net operating losses incurred in tax years beginning after December 31, 2017, may be carried forward indefinitely, but for tax years beginning after December 31, 2020, the deductibility of such federal net operating losses is limited to 80% of taxable income. In addition, the federal and state net operating loss carryforwards and certain tax credits may be subject to significant limitations under Section 382 and Section 383 of the Internal Revenue Code of 1986, as amended, or the Code, respectively, and similar provisions of state law. Under those sections of the Code, if a corporation undergoes an “ownership change,” the corporation’s ability to use its pre-change net operating loss carryforwards and other pre-change attributes, such as research tax credits, to offset its post-change income or tax may be limited. In general, an “ownership change” will occur if there is a cumulative change in our ownership by “5-percent shareholders” that exceeds 50 percentage points over a rolling three-year period. Similar rules may apply under state tax laws. We may have experienced such ownership changes in the past and also may experience ownership changes in the future as a result of future shifts in our share ownership, some of which may be outside of our control. If an ownership change occurs and our ability to use our net operating loss carryforwards and tax credits is materially limited, it would harm our business by effectively increasing our future tax obligations.

In addition, for state income tax purposes, there may be periods during which the use of net operating losses is suspended or otherwise limited, which could accelerate or permanently increase state taxes owed.

Changes in tax law may adversely affect us or our shareholders

The rules dealing with U.S. federal, state and local income taxation are constantly under review by persons involved in the legislative process and by the Internal Revenue Service, or IRS, and the U.S. Treasury Department. The tax treatment of our company is subject to changes in tax laws, regulations and treaties, or the interpretation thereof, tax policy initiatives and reforms under consideration and the practices of tax authorities in jurisdictions in which we operate, as well as tax policy initiatives and reforms related to the Organisation for Economic Co-operation and Development’s, Base Erosion and Profit Shifting, Project, (including “BEPS 2.0”), the European Commission’s state aid investigations and other initiatives. Such changes may include (but are not limited to) the taxation of operating income, investment income, dividends received or (in the specific context of withholding tax) dividends paid, all of which may have retroactive application and could adversely affect our business operations and financial performance. For example, legislation enacted in 2017 (informally titled the Tax Cuts and Jobs Act, the Coronavirus Aid, Relief, and Economic Security Act and the Inflation Reduction Act of 2022) enacted many significant changes to the U.S. tax laws. In addition, under Section 174 of the Internal Revenue Code of 1986, as amended, in taxable years beginning after December 31, 2021, expenses that are incurred for research and development in the United States will be capitalized and subsequently amortized, which may have an adverse effect on our cash flow. The actual impact of this provision will depend on multiple factors, including the amount of research and development expenses we will incur, whether we achieve sufficient income to fully utilize such deductions and whether we conduct our research and development activities inside or outside the United States. Further guidance from the IRS and other tax authorities with respect to such legislation may affect us, and certain aspects of such legislation could be repealed or modified in future legislation. In addition, the Inflation Reduction Act of 2022 includes a minimum tax equal to 15 percent of the adjusted financial statement income of certain corporations, as well as a one percent excise tax on share buybacks. We are unable to predict what tax reform may be proposed or enacted in the future or what effect such changes would have on our business, and it is uncertain if and to what extent various states will conform to federal tax laws. Future tax reform legislation could have a material impact on the value of our deferred tax assets and could increase our future U.S. tax expense. It cannot be

predicted whether, when, in what form, or with what effective dates, tax laws, regulations and rulings may be enacted, promulgated or issued, which could result in an increase in our or our investors' tax liability or require changes in the manner in which we operate in order to minimize or mitigate any adverse effects of changes in tax law.

Tax authorities may disagree with our positions and conclusions regarding certain tax positions, resulting in unanticipated costs, taxes or non-realization of expected benefits.

A tax authority may disagree with tax positions that we have taken, which could result in increased tax liabilities. For example, the U.S. Internal Revenue Service or another tax authority could challenge our allocation of income by tax jurisdiction and the amounts paid between our affiliated companies pursuant to our intercompany arrangements and transfer pricing policies, including amounts paid with respect to our intellectual property development. Similarly, a tax authority could assert that we are subject to tax in a jurisdiction where we believe we have not established a taxable connection, often referred to as a "permanent establishment" under international tax treaties and, such an assertion, if successful, could increase our expected tax liability in one or more jurisdictions. A tax authority may take the position that material income tax liabilities, interest and penalties are payable by us, in which case, we expect that we might contest such assessment. Contesting such an assessment may be lengthy and costly, and if we were unsuccessful in disputing the assessment, the implications could increase our anticipated effective tax rate, where applicable.

United States Holders of our ADSs or ordinary shares may suffer adverse tax consequences if we are characterized as a passive foreign investment company.

Under the U.S. Internal Revenue Code of 1986, as amended, or the Code, we will be a passive foreign investment company, or PFIC, for any taxable year in which, after the application of certain "look-through" rules with respect to subsidiaries, at least 75% of our gross income is passive income, or at least 50% of the value of our assets is attributable to assets that produce passive income or are held for the production of passive income, including cash. For purposes of these tests, passive income includes dividends, interest, gains from commodities and securities transactions, the excess of gains over losses from the disposition of assets which produce passive income (including amounts derived by reason of the temporary investment of funds raised in offerings of our shares) and rents or royalties other than rents or royalties which are received from unrelated parties in connection with the active conduct of a trade or business. If we are characterized as a PFIC for any taxable year during which a United States Holder (as defined below) holds our ADSs or ordinary shares, such United States Holder of ADSs or ordinary shares may suffer adverse tax consequences, including having gains realized on the sale of our ordinary shares treated as ordinary income, rather than capital gain, the loss of the preferential rate applicable to dividends received on our ordinary shares by individuals who are United States Holders, and having interest charges apply to distributions by us and gains from the sales of our shares. As used in this Annual Report, the term "United States Holder" means a beneficial owner of ADSs that is, for U.S. federal income tax purposes, (1) an individual who is a citizen or resident of the United States, (2) a corporation (or entity treated as a corporation for U.S. federal income tax purposes) created or organized in or under the laws of the United States, any state thereof, or the District of Columbia, (3) an estate the income of which is subject to U.S. federal income tax regardless of its source or (4) a trust (x) with respect to which a court within the United States is able to exercise primary supervision over its administration and one or more United States persons have the authority to control all of its substantial decisions or (y) that has elected under applicable U.S. Treasury regulations to be treated as a domestic trust for U.S. federal income tax purposes.

While we cannot express a definitive view about our PFIC status for 2022, based on our current estimates of the composition of our income and valuation of our assets for the taxable year ending December 31, 2022 the manner in which we conduct our business, relevant market data and our current expectations regarding the value and nature of our assets (including our intellectual property) and the sources and nature of our income, we do not believe we were a PFIC for the taxable year ending December 31, 2022. However, no assurances can be provided regarding our PFIC status for 2022 or any other past year, the current year or any future taxable year. Our status as a PFIC is a fact-intensive inquiry made on an annual basis that will depend on the composition of our income and the composition and value of our assets including our intellectual property (which, may be determined in large part by reference to the market value of our ADSs and ordinary shares, which may be volatile) from time to time. The U.S. Internal Revenue Service or courts may not agree with the methodology of our PFIC determination.

Fluctuations in the market price of the ADSs may cause us to become a PFIC for the current or subsequent taxable years because the value of our assets for the purpose of the asset test may be determined by reference to the market price of the ADSs. The composition of our income and assets may also be affected by how, and how quickly, we use our cash and other liquid assets. Because of the uncertainties involved in establishing our PFIC status, our U.S. tax counsel expresses no opinion regarding our PFIC status.

If a United States person is treated as owning at least 10% of the value or voting power of our ordinary shares, including ordinary shares represented by ADSs, such holder may be subject to adverse U.S. federal income tax consequences.

If a United States person is treated as owning (directly, indirectly or constructively) at least 10% of the value or voting power of our ordinary shares, including ordinary shares represented by ADSs, such person may be treated as a “United States shareholder” with respect to each “controlled foreign corporation” in our group (if any), which may subject such person to adverse U.S. federal income tax consequences. Because our group includes at least one U.S. subsidiary, certain of our non-U.S. subsidiaries may be treated as controlled foreign corporations (regardless of whether Ambrx Biopharma Inc. is treated as a controlled foreign corporation). A United States shareholder of a controlled foreign corporation may be required to annually report and include in its United States taxable income its pro rata share of “Subpart F income,” “global intangible low-taxed income” and investments in United States property by controlled foreign corporations, regardless of whether we make any distributions. An individual that is a United States shareholder with respect to a controlled foreign corporation generally would not be allowed certain tax deductions or foreign tax credits that would be allowed to a United States shareholder that is a U.S. corporation. Failure to comply with these reporting and tax paying obligations may subject you to significant monetary penalties and may prevent the statute of limitations with respect to your U.S. federal income tax return for the year for which reporting was due from starting. United States Holders should consult their tax advisors regarding the potential application of these rules to their investment in our ADSs.

We have incurred and will continue to incur costs as a result of operating as a company whose ADSs are publicly traded in the United States, and our management has been and will be required to devote substantial time to compliance initiatives and corporate governance practices, including maintaining an effective system of internal control over financial reporting.

As a public company, we are subject to the reporting requirements of the Exchange Act, the Sarbanes-Oxley Act, the Dodd-Frank Act, as well as rules and regulations subsequently implemented by the SEC, and Nasdaq, our stock exchange, including the establishment and maintenance of effective disclosure and financial controls and changes in corporate governance practices. For example, the Exchange Act requires, among other things, that we file annual, quarterly, and current reports with respect to our business and results of operations. In addition, the rules governing management’s assessment of our internal control over financial reporting are complex and require significant documentation, testing and possible remediation. Compliance with these requirements has increased our legal and financial compliance costs and made some activities more time consuming and costly. In addition, our management and other personnel need to divert attention from operational and other business matters to devote substantial time to these public company requirements. In particular, we expect to continue incurring significant expenses and devote substantial management effort toward ensuring compliance with the requirements of the Sarbanes-Oxley Act. Although we have already hired additional employees to assist us in complying with these requirements, we may need to hire additional accounting and financial staff with appropriate public company experience and technical accounting knowledge, which will increase our operating expenses. In addition, changing laws, regulations, and standards relating to corporate governance and public disclosure create uncertainty for public companies, increasing legal and financial compliance costs, and making some activities more time-consuming. Furthermore, these rules and regulations require us to incur legal and financial compliance costs and make some activities more time-consuming and costly. For example, these rules and regulations make it more difficult and more expensive for us to obtain director and officer liability insurance, and we may be required to accept reduced policy limits and coverage or incur substantially higher costs to obtain the same or similar coverage. As a result, it may be more difficult for us to attract and retain qualified people to serve on our board of directors, our board committees or as executive officers.

Once we cease to be an emerging growth company, we will not be entitled to the exemptions provided in the JOBS Act. After we are no longer an emerging growth company, we expect to incur additional management time and cost to comply with the more stringent reporting requirements applicable to companies that are deemed accelerated filers or large accelerated filers, including complying with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act. If we identify material weaknesses in the future and are unable to comply with the requirements of Section 404 in a timely manner or assert that our internal control over financial reporting is effective, or if our independent registered public accounting firm is unable to express an opinion as to the effectiveness of our internal control over financial reporting once we are no longer an emerging growth company, investors may lose confidence in the accuracy and completeness of our financial reports and the market price of our ADSs could be negatively affected, and we could become subject to investigations by Nasdaq, the SEC or other regulatory authorities, which could require additional financial and management resources. Moreover, we cannot predict or estimate the amount of additional costs we may incur as a result of operating as a public company or the timing of such costs.

We are an “emerging growth company” and as a result of the reduced disclosure and governance requirements applicable to emerging growth companies, our ADSs may be less attractive to investors.

We are an “emerging growth company” as defined in the JOBS Act. For as long as we continue to be an emerging growth company, we may take advantage of exemptions from various reporting requirements that are applicable to other public companies that are not emerging growth companies, including not being required to comply with the auditor attestation requirements of Section 404, exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and shareholder approval of any golden parachute payments not previously approved. We may take advantage of these exemptions until we are no longer an emerging growth company. We could be an emerging growth company until December 31, 2026, although circumstances could cause us to lose that status earlier, including if the aggregate market value of our ordinary shares, including ordinary shares represented by ADSs, held by non-affiliates exceeds \$700 million as of the end of our second fiscal quarter before that time, in which case we would no longer be an emerging growth company as of the following December 31st (the last day of our fiscal year). Investors may find our ADSs less attractive because we may rely on these exemptions. If some investors do find our ADSs less attractive as a result, there may be a less active trading market for our ADSs and the price of our ADSs may be more volatile.

Since shareholder rights under Cayman Islands law differ from those under United States law, you may have difficulty protecting your shareholder rights.

We are an exempted company limited by shares incorporated under the laws of the Cayman Islands. Our corporate affairs are governed by our memorandum and articles of association, the CICA and the common law of the Cayman Islands. The rights of shareholders to take action against our directors, actions by our minority shareholders and the fiduciary responsibilities of our directors to us under Cayman Islands law are to a large extent governed by the common law of the Cayman Islands. The common law of the Cayman Islands is derived in part from comparatively limited judicial precedent in the Cayman Islands as well as from the common law of England, the decisions of whose courts are of persuasive authority, but are not binding, on a court in the Cayman Islands. The rights of our shareholders and the fiduciary responsibilities of our directors under Cayman Islands law are not as clearly established as they would be under statutes or judicial precedent in some jurisdictions in the United States. In particular, the Cayman Islands has a less developed body of securities laws than the United States. Some U.S. states, such as Delaware, have more fully developed and judicially interpreted bodies of corporate law than the Cayman Islands. In addition, Cayman Islands companies may not have standing to initiate a shareholder derivative action in a federal court of the United States.

Shareholders of Cayman Islands exempted companies like us have no general rights under Cayman Islands law to inspect corporate records, other than the memorandum and articles of association and any special resolutions passed by such companies, and the registers of mortgages and charges of such companies. The Registrar of Companies of the Cayman Islands shall make available the list of the names of the current directors of the Company (and where applicable the current alternate directors of the Company) for inspection by any person upon payment of a fee by such person. Our directors have discretion under our memorandum and articles of association to determine whether or not, and under what conditions, our corporate records may be inspected by our shareholders, but are not obliged to make them available to our shareholders. This may make it more difficult for you to obtain the information needed to establish any facts necessary for a shareholder motion or to solicit proxies from other shareholders in connection with a proxy contest.

Certain corporate governance practices in the Cayman Islands, which is our home country, differ significantly from requirements for companies incorporated in other jurisdictions such as the United States. Currently, we do not plan to rely on home country practice with respect to any corporate governance matter. However, if we choose to follow home country practice in the future, our shareholders may be afforded less protection than they otherwise would under rules and regulations applicable to United States domestic issuers. As a result of all of the above, public shareholders may have more difficulty in protecting their interests in the face of actions taken by our management, members of our board of directors or our controlling shareholders than they would as public shareholders of a company incorporated in the United States.

Provisions in our amended and restated memorandum and articles of association may prevent or frustrate attempts by our shareholders to change our management and hinder efforts to acquire a controlling interest in us, and the market price of our ADSs may be lower as a result.

There are provisions in our amended and restated memorandum and articles of association that may make it difficult for a third party to acquire, or attempt to acquire, control of our company, even if a change of control was considered favorable by you and other shareholders. For example, our board of directors has the authority to issue shares of an additional class or classes of shares, which could include preference shares. The board of directors can fix the price, rights, preferences, privileges, and restrictions of the other classes of shares without any further vote or action by our shareholders. The issuance of such shares may delay or prevent a change of control transaction. As a result, the market price of our ADSs and the voting and other rights of our shareholders may be adversely affected. An issuance of other classes of shares may result in the loss of voting control to other shareholders.

Our amended and restated memorandum and articles of association also contain other provisions that could have an anti-takeover effect, including:

- only one of our three classes of directors will be elected each year;
- shareholders are entitled to remove directors only for cause;
- shareholders are not permitted to take actions by written consent; and
- shareholders must give advance notice to nominate directors or submit proposals for consideration at annual general meetings.

These provisions could discourage potential acquisition proposals and could delay or prevent a change of control transaction. They could also have the effect of discouraging others from making tender offers, including transactions that may be in your best interests. These provisions may also prevent changes in our management or limit the price that investors are willing to pay for our ADSs.

You may be subject to limitations on transfers of your ADSs.

Your ADSs are transferable on the books of the depositary. However, the depositary may close its transfer books at any time or from time to time when deemed necessary or advisable by it in good faith in connection with the performance of its duties or at our reasonable written request, subject in all cases to compliance with applicable U.S. securities laws. In addition, the depositary may refuse to deliver, transfer or register transfers of ADSs generally when our books or the books of the depositary are closed, or at any time if we or the depositary deems it advisable to do so because of any requirement of law or of any government or governmental body, or under any provision of the deposit agreement, or for any other reason.

General Risk Factors

Failure to build our finance infrastructure and improve our accounting systems and controls could impair our ability to comply with the financial reporting and internal controls requirements for publicly traded companies.

We operate in an increasingly demanding regulatory environment, which requires us to comply with the Sarbanes-Oxley Act, the regulations of Nasdaq, the rules and regulations of the SEC, expanded disclosure requirements, accelerated reporting requirements and more complex accounting rules. Company responsibilities required by the Sarbanes-Oxley Act include establishing corporate oversight and adequate internal control over financial reporting and disclosure controls and procedures. Effective internal controls are necessary for us to produce reliable financial reports and are important to help prevent financial fraud.

We anticipate that the process of building our accounting and financial functions and infrastructure will require significant additional professional fees, internal costs and management efforts. We expect that we will need to implement a new internal system to combine and streamline the management of our financial, accounting, human resources and other functions. However, such a system would likely require us to complete many processes and procedures for the effective use of the system or to run our business using the system, which may result in substantial costs. Any disruptions or difficulties in implementing or using such a system could adversely affect our controls and harm our business. Moreover, such disruption or difficulties could result in unanticipated costs and diversion of management attention. In addition, we may discover weaknesses in our system of internal financial and accounting controls and procedures that could result in a material misstatement of our financial statements. Our internal control over financial reporting will not prevent or detect all errors and all fraud. A control system, no matter how well designed and operated, can provide only reasonable, not absolute, assurance that the control system's objectives will be met. Because of the inherent limitations in all control systems, no evaluation of controls can provide absolute assurance that misstatements due to error or fraud will not occur or that all control issues and instances of fraud will be detected.

If we are not able to comply with the requirements of Section 404 of the Sarbanes-Oxley Act in a timely manner, or if we are unable to maintain proper and effective internal controls, we may not be able to produce timely and accurate financial statements. If we cannot provide reliable financial reports or prevent fraud, our business and results of operations could be harmed, investors could lose confidence in our reported financial information and we could be subject to sanctions or investigations by Nasdaq, the SEC or other regulatory authorities.

If we are unable to maintain effective internal controls, our business, financial position and results of operations could be adversely affected.

We are subject to reporting and other obligations under the Exchange Act, including the requirements of Section 404 of the Sarbanes-Oxley Act, which require annual management assessments of the effectiveness of our internal control over financial reporting.

The rules governing the standards that must be met for management to determine that our internal control over financial reporting is effective are complex and require significant documentation, testing and possible remediation to meet the detailed standards under the rules. During the course of its testing, our management may identify material weaknesses or deficiencies which may not be remedied in time to meet the deadline imposed by the Sarbanes-Oxley Act. These reporting and other obligations place significant demands on our management and administrative and operational resources, including accounting resources.

Our management is responsible for establishing and maintaining adequate internal control over financial reporting. Our internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with accounting principles generally accepted in the United States. Any failure to maintain effective internal controls could have an adverse effect on our business, financial position and results of operations.

Our disclosure controls and procedures may not prevent or detect all errors or acts of fraud.

We are subject to the periodic reporting requirements of the Exchange Act. We designed our disclosure controls and procedures to reasonably assure that information we must disclose in reports we file or submit under the Exchange Act is accumulated and communicated to management, and recorded, processed, summarized and reported within the time periods specified in the rules and forms of the SEC. We believe that any disclosure controls and procedures or internal controls and procedures, no matter how well-conceived and operated, can provide only reasonable, not absolute, assurance that the objectives of the control system are met.

These inherent limitations include the realities that judgments in decision-making can be faulty, and that breakdowns can occur because of simple error or mistake. For example, our directors or executive officers could inadvertently fail to disclose a new relationship or arrangement causing us to fail to make any related party transaction disclosures. Additionally, controls can be circumvented by the individual acts of some persons, by collusion of two or more people or by an unauthorized override of the controls. Accordingly, because of the inherent limitations in our control system, misstatements due to error or fraud may occur and not be detected.

Future changes in financial accounting standards or practices may cause adverse and unexpected revenue fluctuations and adversely affect our reported results of operations.

Future changes in financial accounting standards may cause adverse, unexpected revenue fluctuations and affect our reported financial position or results of operations. Financial accounting standards in the United States are constantly under review and new pronouncements and varying interpretations of pronouncements have occurred with frequency in the past and are expected to occur again in the future. As a result, we may be required to make changes in our accounting policies. Those changes could affect our financial condition and results of operations or the way in which such financial condition and results of operations are reported. We have invested resources to comply with evolving standards, and this investment may result in increased general and administrative expenses and a diversion of management time and attention from business activities to compliance activities.

Unstable market and economic conditions may have serious adverse consequences on our business and financial condition and the trading price of our ADSs.

The global credit and financial markets have recently experienced extreme volatility and disruptions, including severely diminished liquidity and credit availability, declines in consumer confidence, declines in economic growth, increases in unemployment rates and uncertainty about economic stability. This is as a result of a number of factors, including the COVID-19 pandemic (and actions taken to slow its spread) and the ongoing conflict between Ukraine and Russia. Further deterioration in credit and financial markets and confidence in economic conditions may occur. Our general business strategy may be adversely affected by any such economic downturn, volatile business environment or continued unpredictable and unstable market conditions. If the current equity and credit markets deteriorate, it may make any necessary debt or equity financing more difficult, more costly and more dilutive. Failure to secure any necessary financing in a timely manner and on favorable terms could have a material adverse effect on our growth strategy, financial performance and share price and could require us to delay or abandon clinical development plans. In addition, there is a risk that one or more of our current service providers, manufacturers and other partners may not survive an economic downturn, which could directly affect our ability to attain our operating goals on schedule and on budget. Any of these events could have a material and negative impact on the trading price of our ADSs.

If equity research analysts do not publish research or reports, cease publishing research reports, or publish unfavorable research or reports, about us, our business or our market, the price and trading volume of our ADSs could decline.

The trading market for our ADSs is influenced by the research and reports that equity research analysts publish about us and our business. Certain equity research analysts may never provide research coverage of our ADSs, and such lack of research coverage may adversely affect the market price of our ADSs. With respect to equity research analysts that do cover our ADSs, we do not have any control over the analysts or the content and opinions included in their reports. The price of our ADSs could decline if one or more equity research analysts downgrade our ADSs or issue other unfavorable commentary or research about us. If one or more equity research analysts cease coverage of us or fail to publish reports on us regularly, demand for our ADSs could decrease, which in turn could cause the trading price or trading volume of our ADSs to decline.

We could be subject to securities class action litigation.

In the past, securities class action litigation has often been brought against a company following a decline in the market price of its securities. This risk is especially relevant for us because pharmaceutical companies have experienced significant stock price volatility in recent years. If we face such litigation, it could result in substantial costs and a diversion of management's attention and resources, which could harm our business.

If our information technology systems or data, or those of third parties upon which we rely, are or were compromised, we could experience adverse consequences resulting from such compromise, including but not limited to regulatory investigations or actions; litigation; fines and penalties; disruptions of our business operation (including related to our product candidate development programs); reputational harm; loss of revenue or profits; and other adverse consequences.

We are increasingly dependent upon information technology systems, infrastructure and data to operate our business. In the ordinary course of business, we process confidential information (including but not limited to intellectual property, proprietary business information and personal information). It is critical that we do so in a secure manner to maintain the confidentiality and integrity of such confidential information.

Our internal information technology systems and those of our third-party CROs and other contractors and consultants, as well as our confidential information, are potentially vulnerable to breakdown or other damage or interruption from service interruptions, system malfunction, natural disasters, terrorism, war and telecommunication and electrical failures, as well as security breaches cyberattacks by malicious third parties (including the deployment of harmful malware, ransomware, denial-of-service attacks, social engineering, supply-chain attacks, software bugs, credential harvesting, and other threats confidential information), which may compromise the confidentiality, integrity and availability of our confidential information. In particular, severe ransomware attacks are becoming increasingly prevalent and can lead to significant interruptions in our operations, loss of sensitive data and income, reputational harm, and diversion of funds. Extortion payments may alleviate the negative impact of a ransomware attack, but we may be unwilling or unable to make such payments due to, for example, applicable laws or regulations prohibiting such payments.

These threats are prevalent and continue to rise, are increasingly difficult to detect, and come from a variety of sources, including traditional computer "hackers," threat actors, "hacktivists," organized criminal threat actors, personnel (such as through theft or misuse), sophisticated nation states, and nation-state-supported actors. Some actors now engage and are expected to continue to engage in cyberattacks, including without limitation nation-state actors for geopolitical reasons and in conjunction with military conflicts and defense activities. During times of war and other major conflicts, we and our third-party CROs and other contractors and consultants may be vulnerable to a heightened risk of these attacks, including retaliatory cyberattacks, that could materially disrupt our systems and operations, supply chain, and ability to produce, sell and distribute our goods and services. For example, there has been an increase in phishing and spam emails as well as social engineering attempts from "hackers" hoping to use the recent developments in Ukraine to their advantage. Remote work has become more common and has increased risks to our information technology systems and data, as more of our employees utilize network connections, computers and devices outside our premises or network, including working at home, while in transit and in public locations.

Additionally, future or past business transactions (such as acquisitions or integrations) could expose us to additional cybersecurity risks and vulnerabilities, as our systems could be negatively affected by vulnerabilities present in acquired or integrated entities' systems and technologies. Furthermore, we may discover security issues that were not found during due diligence of such acquired or integrated entities, and it may be difficult to integrate companies into our information technology environment and security program.

We also have outsourced elements of our operations to third parties, and as a result we manage a number of third-party contractors and other third parties who process our confidential information. We rely on these third parties to operate critical business systems to process confidential information in a variety of contexts, including, without limitation, cloud-based infrastructure, data center facilities, encryption and authentication technology, employee email, and other functions. Our ability to monitor these third parties' information security practices is limited, and these third parties may not have adequate information security measures in place. If our third-party service providers experience a security incident or other interruption, we could experience adverse consequences. While we may be entitled to damages if our third-party service providers fail to satisfy their privacy or security-related obligations to us, any award may be insufficient to cover our damages, or we may be unable to recover such award. In addition, supply-chain attacks have increased in frequency and severity, and we cannot guarantee that third parties' infrastructure in our supply chain or our third-party partners' supply chains have not been compromised.

We may expend significant resources or modify our business activities (including our clinical trial activities) to try to protect against security incidents. Certain data privacy and security obligations may require us to implement and maintain specific security measures or industry-standard or reasonable security measures to protect our information technology systems and confidential information.

Our data protection efforts and our investment in information technology may not prevent significant breakdowns, data leakages, breaches in our systems or other cyber incidents. We take steps to detect and remediate vulnerabilities, but we may not be able to detect and remediate all vulnerabilities because the threats and techniques used to exploit the vulnerability change frequently and are often sophisticated in nature. Therefore, such vulnerabilities could be exploited but may not be detected until after a security incident has occurred. These vulnerabilities pose material risks to our business. Further, we may experience delays in developing and deploying remedial measures designed to address any such identified vulnerabilities. For example, if a security breach or other event were to occur and cause interruptions in our operations or the confidentiality, integrity and availability of our confidential information, it could result in a material disruption of our programs and the development of our product candidates could be delayed. In addition, the loss of clinical trial data for our product candidates could result in delays in our marketing approval efforts and significantly increase our costs to recover or reproduce the data. Furthermore, significant disruptions of our internal information technology systems or security breaches could result in the loss, misappropriation, and/or unauthorized access, use, or disclosure of, or the prevention of access to, confidential information, which could result in financial, legal, business, and reputational harm to us. For example, any such event could harm our reputation directly, compel us to comply with federal and/or state breach notification laws and foreign law equivalents, subject us to mandatory corrective action, subject us to government enforcement actions or litigation, expose us to negative publicity, and otherwise subject us to liability under relevant laws and regulations, which could result in significant legal and financial exposure and reputational damages that could potentially have an adverse effect on our business. Additionally, theft of our intellectual property or proprietary business information could require substantial expenditures to remedy.

Our contracts may not contain limitations of liability, and even where they do, the limitations of liability in our contracts may not be sufficient to protect us from liabilities, damages, or claims related to our data privacy and security obligations. Our insurance coverage may not be adequate or sufficient to protect us from or to mitigate liabilities arising out of our privacy and security practices, such coverage may not continue to be available on commercially reasonable terms or at all, and such coverage may not pay future claims. In addition to experiencing a security incident, third parties may gather, collect, or infer sensitive information about us from public sources, data brokers, or other means that reveals competitively sensitive details about our organization and could be used to undermine our competitive advantage or market position.

We or the third parties upon whom we depend may be adversely affected by earthquakes, fires or other natural disasters and our business continuity and disaster recovery plans may not adequately protect us from a serious disaster.

Our headquarters and main research facility are located in San Diego, California, which in the past has experienced severe earthquakes and fires. If these earthquakes, fires, other natural disasters, terrorism and similar unforeseen events beyond our control prevented us from using all or a significant portion of our headquarters or research facility, it may be difficult or, in certain cases, impossible for us to continue our business for a substantial period of time. We do not have a disaster recovery or business continuity plan in place and may incur substantial expenses as a result of the absence or limited nature of our internal or third-party service provider disaster recovery and business continuity plans, which, particularly when taken together with our lack of earthquake insurance, could have a material adverse effect on our business. Furthermore, integral parties in our supply chain are operating from single sites, increasing their vulnerability to natural disasters or other sudden, unforeseen and severe adverse events. If such an event were to affect our supply chain, it could have a material adverse effect on our ability to conduct our clinical trials, our development plans and business.

We are subject to certain United States and foreign anti-corruption, anti-money laundering, export control, sanctions, and other trade laws and regulations. We can face serious consequences for violations.

United States and foreign anti-corruption, anti-money laundering, export control, sanctions, and other trade laws and regulations, or collectively, Trade Laws, prohibit, among other things, companies and their employees, agents, CROs, legal counsel, accountants, consultants, contractors, and other partners from authorizing, promising, offering, providing, soliciting, or receiving directly or indirectly, corrupt or improper payments or anything else of value to or from recipients in the public or private sector. Violations of Trade Laws can result in substantial criminal fines and civil penalties, imprisonment, the loss of trade privileges, debarment, tax reassessments, breach of contract and fraud litigation, reputational harm, and other consequences. We have direct or indirect interactions with officials and employees of government agencies or government-affiliated hospitals, universities, and other organizations. We also expect our non-U.S. activities to increase over time. We expect to rely on third parties for research, preclinical studies, and clinical trials and/or to obtain necessary permits, licenses, patent registrations, and other marketing approvals. We can be held liable for the corrupt or other illegal activities of our personnel, agents, or partners, even if we do not explicitly authorize or have prior knowledge of such activities.

If we fail to comply with environmental, health and safety laws and regulations, we could become subject to fines or penalties or incur costs that could have a material adverse effect on the success of our business.

We, and the third parties with whom we share our facilities, are subject to numerous environmental, health and safety laws and regulations, including those governing laboratory procedures and the handling, use, storage, treatment and disposal of hazardous materials and wastes. Each of our operations involve the use of hazardous and flammable materials, including chemicals and biological materials. Each of our operations also produce hazardous waste products. We generally contract with third parties for the disposal of these materials and wastes. We cannot eliminate the risk of contamination or injury from these materials. We could be held liable for any resulting damages in the event of contamination or injury resulting from the use of hazardous materials by us or the third parties with whom we share our facilities, and any liability could exceed our resources. We also could incur significant costs associated with civil or criminal fines and penalties.

Although we maintain workers' compensation insurance to cover us for costs and expenses, we may incur due to injuries to our employees resulting from the use of hazardous materials, this insurance may not provide adequate coverage against potential liabilities. We do not maintain insurance for environmental liability or toxic tort claims that may be asserted against us in connection with our storage or disposal of biological, or hazardous materials.

In addition, we may incur substantial costs in order to comply with current or future environmental, health and safety laws and regulations. These current or future laws and regulations may impair our research and development. Failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions.

Item 1B. Unresolved Staff Comments.

None.

Item 2. Properties.

Our principal executive offices are currently located at 10975 North Torrey Pines Road, La Jolla, California 92037, where we lease an approximately 36,000 square foot facility, used as laboratory, research and office space. We believe that our current facilities are suitable and adequate to meet our current needs.

Item 3. Legal Proceedings.

From time to time we may be involved in various disputes and litigation matters that arise in the ordinary course of business activities. We are currently not a party to any material legal proceedings.

Item 4. Mine Safety Disclosures.

Not applicable.

PART II

Item 5. Market for Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities.

Market Information

Our ADSs began trading on the New York Stock Exchange, or NYSE, on June 17, 2021 under the trading symbol "AMAM". Prior to that date, there was no public trading market for our ADSs. On March 16, 2023, our ADSs ceased trading on the NYSE and on March 17, 2023, began trading on the Nasdaq Global Select Market under the trading symbol "AMAM".

Holders of Record

As of March 20, 2023, there were 386,486,014 of our ordinary shares outstanding and 38 holders of record of our ordinary shares. This number was derived from our shareholder records and does not include beneficial owners of our ordinary shares whose shares are held in the name of various dealers, clearing agencies, banks, brokers and other fiduciaries.

Our ordinary shares may be represented by ADSs. Each ADS represents seven of our ordinary shares.

Dividend Policy

We have never paid cash dividends on our ordinary shares and we do not have any present plan to pay any cash dividends on our ordinary shares in the foreseeable future. We currently intend to retain most, if not all, of our available funds and any future earnings to operate and expand our business.

Our board of directors has discretion over whether to distribute dividends, subject to the amended and restated memorandum and articles of association of our company and certain requirements of Cayman Islands law. In addition, our shareholders may declare dividends by ordinary resolution, but no dividend shall exceed the amount recommended by our directors. All dividends are subject to certain restrictions under Cayman Islands law, namely that we may only pay dividends out of profits or the credit standing in our share premium account, and provided always that in no circumstances may a dividend be paid if it would result in our inability to pay our debts as they fall due in the ordinary course of business immediately following the date on which the distribution or dividend is paid. Even if we decide to pay dividends, the form, frequency and amount will depend upon our future operations and earnings, capital requirements and surplus, general financial condition, contractual restrictions and other factors that our board of directors may deem relevant.

If we pay any dividends on our ordinary shares, we will pay those dividends which are payable in respect of the ordinary shares underlying the ADSs to the depositary, as the registered holder of such ordinary shares, and the depositary then will pay such amounts to our ADS holders in proportion to the ordinary shares underlying the ADSs held by such ADS holders, subject to the terms of the deposit agreement, including the fees and expenses payable thereunder.

Securities Authorized for Issuance Under Equity Compensation Plans

See Item 12 of Part III of this Annual Report for information about our equity compensation plans, which is incorporated by reference herein.

Recent Sales of Unregistered Securities

None.

Issuer Repurchases of Equity Securities

None.

Use of Proceeds

On June 17, 2021, we sold 7,000,000 ADSs, representing 49,000,000 of our ordinary shares, in connection with our initial public offering, or the IPO, and on July 7, 2021, we sold an additional 892,831 ADSs, representing 6,249,817 of our ordinary shares, pursuant to the underwriters' partial exercise of their over-allotment option, each at a public offering price of \$18.00 per ADS for an aggregate offering price of approximately \$142.1 million. The offer and sale of all the ADSs in the IPO were registered under the Securities Act pursuant to a registration statement on Form F-1 (File No. 333-256639) that was declared effective by the U.S. Securities and Exchange Commission, or SEC, on June 17, 2021. There has been no material change in the use of proceeds from our IPO as described in our final prospectus filed with the SEC pursuant to Rule 424(b)(4) on June 21, 2021.

Item 6. [RESERVED]

Not applicable.

Item 7. Management's Discussion and Analysis of Financial Condition and Results of Operations.

The following discussion and analysis of our financial condition and results of operations should be read together with our consolidated financial statements and the notes thereto appearing elsewhere in this Annual Report. Some of the information contained in this discussion and analysis or set forth elsewhere in this Annual Report, including information with respect to our plans and strategy for our business and related financing, includes forward-looking statements that involve risks and uncertainties. As a result of many factors, including those set forth in the section titled "Item 1A. Risk Factors" of this Annual Report, our actual results could differ materially from the results described in or implied by these forward-looking statements. Please also see the section titled "Cautionary Statement Regarding Forward-Looking Statements."

Our discussion and analysis below is focused on our financial condition and results of operations for the years ended December 31, 2022 and 2021, including year-over-year comparisons for these years. Discussion and analysis of our financial condition and results of operations for the year ended December 31, 2021, as well as the year-over-year comparisons for the years ended December 31, 2021 and 2020, is located in the section titled "Item 5. Operating and Financial Review and Prospects" included in our Annual Report on Form 20-F filed with the U.S. Securities and Exchange Commission, or SEC, on April 26, 2022, which specific discussion and analysis is incorporated herein by reference.

Overview

We are a clinical-stage biologics company focused on discovering and developing a novel class of engineered precision biologics using our proprietary expanded genetic code technology platform that allows us to incorporate, in a site-specific manner, synthetic amino acids into proteins within living cells. Our product candidates are designed to overcome the inherent limitations of conventional conjugation approaches that use natural amino acids for non-site-specific conjugation, offering potential safety and efficacy benefits to treat patients across multiple therapeutic areas. We believe that our technology allows us to engineer a single optimized structure by designing the conjugation chemistries, selecting the precise number of amino acids and conjugation positions in the protein, and expanding the types of payloads that can be conjugated. Our precision engineering capabilities and the broad applicability of our expanded genetic code technology platform have the potential to enhance and enable the therapeutic functions of conventional biologics and bio-conjugates.

Our primary focus is on two lead ADC product candidates in clinical development: ARX788 and ARX517. ARX788, our most advanced product candidate, is an anti-HER2 ADC currently being studied in breast, gastric and other solid tumor trials. The most advanced trial is an ongoing Phase 3 clinical trial for HER2-positive metastatic breast cancer being conducted in China by our partner. We received Fast Track designation from the U.S. Food and Drug Administration, or FDA, for ARX788 as a monotherapy for the treatment of HER2-positive metastatic breast cancer patients who have received one or more prior anti-HER2-based regimens in the metastatic setting. ARX517, our second most advanced product candidate, is an anti-PSMA ADC currently being studied in an open-label Phase 1 clinical trial evaluating the safety and preliminary efficacy of ARX517 in the treatment of advanced prostate cancer, including metastatic castration-resistant prostate cancer. We believe that ARX517, if ultimately approved, has the potential to be a first-in-class ADC targeting PSMA.

Research and Development Agreements

For a summary of the key terms for certain of our collaborative research and development agreements, see "Item 1. Business Overview—Research and Development Agreements" within this Annual Report.

Components of Results of Operations

Revenue

To date, we have not generated any revenue from product sales and do not expect to generate any revenue from product sales in the foreseeable future. We record revenue from research and development agreements, or R&D Agreements, including amounts related to upfront payments for license fees, reimbursements, milestones and other contingent payments and payments for research and development services. Our ability to generate product revenue and to become profitable will depend upon our ability to successfully develop, obtain regulatory approval and commercialize our product candidates. Because of the numerous risks and uncertainties associated with product development and regulatory approval, we are unable to predict the amount, timing or whether we will be able to obtain product revenue.

Operating Expenses

Research and Development

Research and development expenses consist primarily of direct and indirect costs incurred in connection with the development of our technology platform, product candidates, discovery efforts and preclinical and clinical development of our product candidates.

Our direct costs include the following external costs:

- expenses incurred under agreements with third parties, including contract research organizations, or CROs, and other third parties conducting preclinical research and development activities and clinical trials on our behalf;
- costs of developing and scaling our manufacturing process and manufacturing drug products for use in our preclinical studies and future clinical trials, including the costs of contract manufacturing organizations, or CMOs, that will manufacture our clinical trial material for use in our preclinical studies and potential future clinical trials;
- costs of outside consultants, including their fees and related travel expenses;
- costs of laboratory supplies and acquiring, developing and manufacturing preclinical study and clinical trial materials; and
- license payments for intellectual property used in research and development activities.

Our indirect costs include the following internal costs:

- personnel costs, which include salaries, benefits and other employee related costs, including share-based compensation, for personnel engaged in research and development functions; and
- facility, depreciation, amortization and equipment related costs, which include depreciation and amortization costs and expenses for rent and maintenance of facilities and other operating costs if specifically, identifiable to research and development activities.

We expense research and development costs as incurred. Research and development activities are central to our business model. In-licensing fees and other costs to acquire technologies used in research and development that have not yet received regulatory approval and that are not expected to have an alternative future use are expensed when incurred. We track direct costs by stage of program, clinical or preclinical. However, we do not track indirect costs on a program specific or stage of program basis because these costs are deployed across multiple programs and, as such, are not separately classified.

We expect research and development expenses will continue to increase substantially for the foreseeable future and will comprise a larger percentage of our total expenses as we conduct clinical trials for our current product candidates in development, and continue to discover and develop additional candidates.

As of the date of this Annual Report, we cannot reasonably determine the timing of initiation, the duration or the completion costs of future clinical trials and preclinical studies of product candidates due to the inherently unpredictable nature of preclinical and clinical development. Clinical and preclinical development timelines, the probability of success and development costs can differ materially from expectations. We anticipate that we will make determinations as to which product candidates and development programs to pursue and how much funding to direct to each product candidate or program on an ongoing basis in response to the results of ongoing and future preclinical studies and clinical trials, regulatory developments and our ongoing assessments as to each product candidate's commercial potential. We will need to raise substantial additional capital in the future. In addition, we cannot forecast which product candidates may be subject to future collaborations, when such arrangements will be secured, if at all, and to what degree such arrangements would affect our development plans and capital requirements. We may never succeed in obtaining marketing approval for any product candidate.

Our future research and development costs may vary significantly based on a wide variety of factors, such as:

- the scope, rate of progress, expense and results of ongoing preclinical and clinical development activities, including clinical trials of ARX788 and ARX517, as well as of any future clinical trials of other product candidates, and other additional research and development activities we may conduct;
- uncertainties in clinical trial design;
- per patient trial costs;
- the number of trials required for approval;
- the number of sites included in the trials;
- the number of patients that participate in the trials;
- the countries in which the trials are conducted;
- the length of time required to enroll eligible patients;
- the drop-out or discontinuation rates of patients, particularly in light of the continued COVID-19 pandemic environment;
- the safety and efficacy profiles of our product candidates;
- the timing receipt, and terms of any approvals from applicable regulatory authorities including the FDA and non-U.S. regulators;
- maintaining a continued acceptable safety profile of our product candidates following approval, if any, of our product candidates;
- significant and changing government regulation and regulatory guidance;
- establishing clinical and commercial manufacturing capabilities or making arrangements with third-party manufacturers in order to ensure that we or our third-party manufacturers are able to make product successfully;
- the impact of any business interruptions to our operations or to those of the third parties with whom we work, particularly considering the COVID-19 pandemic environment, the ongoing conflict between Ukraine and Russia and other geopolitical and macroeconomic conditions and the recent disruption in access to bank deposits and lending commitments due to bank failures;
- the expense of filing, prosecuting, defending, and enforcing any patent claims and other intellectual property rights; and
- the extent to which we establish additional strategic collaborations or other arrangements.

A change in the outcome of any of these variables with respect to the development of any of our product candidates could significantly change the costs and timing associated with the development of that product candidate. For example, if the FDA or non-U.S. regulators were to require us to conduct clinical trials beyond those that we anticipate will be required for the completion of clinical development of a product candidate, or if we

experience significant delays in our clinical trials due to slower than expected patient enrollment or other reasons, we would be required to expend significant additional financial resources and time on the completion of clinical development.

The process of conducting the necessary preclinical and clinical research to obtain regulatory approval is costly and time-consuming. The actual probability of success for our product candidates may be affected by a variety of factors. We may never succeed in achieving regulatory approval for any of our product candidates. Further, several factors, including those outside of our control, could adversely impact the timing and duration of our product candidates' development, which could increase our research and development expenses.

General and Administrative Expenses

General and administrative expenses consist primarily of personnel costs, which include salaries and other related costs, including share-based compensation, for personnel in our executive, finance, business development, operations and administrative functions. General and administrative expenses also include legal fees relating to intellectual property and corporate matters; professional fees for accounting, auditing, tax and consulting services; insurance costs; travel expenses; facilities-related costs, which include direct depreciation costs and expenses for rent and maintenance of facilities and other operating costs that are not specifically attributable to research activities.

Our general and administrative expenses are anticipated to increase in the future as we increase our personnel headcount to support our continued research activities and development of our product candidates and incur increased expenses associated with being a public company, including costs of accounting, audit, legal, regulatory and tax-related services associated with maintaining compliance with the Nasdaq Global Select Market, or Nasdaq, and the U.S. Securities and Exchange Commission, or SEC, requirements; director and officer insurance costs; and investor and public relations costs.

Results of Operations

Results of Operations for the Years Ended December 31, 2022 and 2021

The following table summarizes our results of operations in for the periods presented (in thousands):

	2022	2021	\$ Change	% Change
Revenues	\$ 7,402	\$ 7,455	\$ (53)	(0.7%)
Operating expenses:				
Research and development	53,307	54,295	(988)	(1.8%)
General and administrative	20,836	17,071	3,765	22.1%
Impairment of intangible assets	9,660	513	9,147	1,783.0%
Total operating expenses	83,803	71,879	11,924	16.6%
Loss from operations	(76,401)	(64,424)	(11,977)	18.6%
Other income (expense), net:				
Investment income, net	1,337	—	1,337	—
Interest expense, net	(968)	—	(968)	—
Other (expense) income, net	(27)	40	(67)	(167.5%)
Change in fair value of redeemable noncontrolling interests	—	(3,903)	3,903	(100.0%)
Total other income (expense), net	342	(3,863)	4,205	(108.9%)
Loss before provision for income taxes	(76,059)	(68,287)	(7,772)	11.4%
Provision for income taxes	(1,937)	(1)	(1,936)	193,600.0%
Net loss	<u>\$ (77,996)</u>	<u>\$ (68,288)</u>	<u>\$ (9,708)</u>	14.2%

Revenues

The change in revenue was minimal during the periods presented, and consisted of the following (in thousands):

	2022	2021	\$ Change	% Change
License fees	\$ 3,442	\$ 3,533	\$ (91)	(2.6%)
Research and development services	2,140	2,072	68	3.3%
Milestones	1,000	—	1,000	—
Reimbursements	820	1,850	(1,030)	(55.7%)
Total revenues	<u>\$ 7,402</u>	<u>\$ 7,455</u>	<u>\$ (53)</u>	<u>(0.7%)</u>

Research and Development Expenses

The following table summarizes our research and development expenses for the periods presented (in thousands):

	2022	2021	\$ Change	% Change
Direct costs:				
Clinical programs	\$ 24,159	\$ 21,912	\$ 2,247	10.3%
Preclinical programs	4,325	3,816	509	13.3%
Indirect costs:				
Personnel and related costs	18,755	23,153	(4,398)	(19.0%)
Facility, depreciation, amortization and equipment related	6,068	5,414	654	12.1%
Total research and development expenses	<u>\$ 53,307</u>	<u>\$ 54,295</u>	<u>\$ (988)</u>	<u>(1.8%)</u>

Research and development expenses decreased by 1.8%, or \$1.0 million, due primarily to a net decrease of \$4.4 million in personnel related costs mainly associated with a \$5.4 million reduction in share-based compensation expense related to accelerated vesting of certain options in 2021 upon the closing of our IPO, partially offset by \$0.8 million of severance costs associated with a reduction in our workforce as a result of our strategic reprioritization announced in October 2022. Clinical costs increased by \$2.2 million due primarily to higher costs of \$3.6 million associated with our ARX517 product candidate offset in part by a \$1.3 million decrease related to company-sponsored clinical trials for ARX788.

General and Administrative Expenses

General and administrative expenses increased by 22.1%, or \$3.8 million, due primarily to increases of \$2.0 million in personnel costs and \$1.7 million in other general and administrative costs. The increase in personnel costs was driven primarily by higher compensation related costs, including retention costs for key employees and severance costs associated with a reduction in our workforce as a result of our strategic reprioritization announced in October 2022. The increase in other general and administrative costs was driven primarily by increases in legal, consulting and insurance costs of \$2.2 million as a result of operating as a public company, offset in part by a decrease related to audit and tax fees of \$0.5 million.

Impairment of intangible assets

During the year ended December 31, 2022, we received notices of termination from Bristol-Myers Squibb Company, or BMS, related to our Relaxin and FGF-21 definite-lived intangible assets, which we acquired in July 2015. Due to the termination notices and our determination that the definite-lived intangible assets had no alternative future use, we concluded the net carrying value of the assets was greater than their estimated fair values and therefore recorded impairment charges of \$2.5 million and \$7.2 million, respectively.

During the year ended December 31, 2021, we recorded an impairment charge of \$0.5 million related to other definite-lived intangible assets acquired in July 2015, due to our determination that the carrying value of the acquired technology exceeded the estimated future cash flows.

For additional details regarding our intangible assets and related impairments see the sections titled *Intangible Assets, Net of Note 2—Summary of Significant Accounting Policies* and *Note 4—Intangible Assets, Net*, to our consolidated financial statements and related notes included elsewhere in this Annual Report.

Other Income (Expense), net

During the year ended December 31, 2022, other income, net, was primarily related to investment income, net of \$1.3 million, offset in part by interest expense, net, of \$1.0 million. During the second quarter of 2022 we purchased marketable debt securities, available-for-sale, or MDS, including commercial paper, U.S. government securities, debt securities of U.S. financial institutions, corporate debt and asset backed securities. Investment income is comprised of (i) interest and dividend income, (ii) the net impact of amortization and accretion associated with premiums and discounts incurred at the time of purchase, and to a lesser extent, (iii) realized gains and losses on sales of MDS. Interest expense, net, was primarily due to borrowings made pursuant a short-term bridge loan which was issued and repaid during the first quarter of 2022.

During the year ended December 31, 2021, other expense, net, was primarily related to a change in fair value associated with the reclassification of our redeemable noncontrolling interest to a liability prior to its settlement in the second quarter of 2021.

For additional details regarding our MDS see the sections titled *Marketable Debt Securities, Available-for-Sale subsection of Note 2—Summary of Significant Accounting Policies* and *Note 5—Marketable Debt Securities, Available-for-Sale*, to our consolidated financial statements and related notes included elsewhere in this Annual Report.

Liquidity and Capital Resources

Overview

As of December 31, 2022, we had cash, cash equivalents and MDS of \$101.3 million, of which \$16.8 million are non-current MDS. Based on our current operating plan, we believe our existing cash, cash equivalents and MDS will enable us to fund our operating expenses and capital requirements for at least the next 12 months from the date of this Annual Report.

On July 29, 2022, we entered into an at-the-market sales agreement with Cowen and Company LLC, pursuant to which we were able to offer and sell our ADSs, each representing seven of our ordinary shares, having an aggregate offering price of up to \$80.0 million (the ATM Program). During the first quarter of 2023, we issued and sold 16,575,826 of our ADSs at an average selling price of \$4.83 per ADS, for gross proceeds of approximately \$80.0 million, less sales commissions of approximately \$2.0 million, for net proceeds of approximately \$78.0 million. Accordingly, as of March 10, 2023, the ATM Program is complete.

Since inception, we have invested most of our resources in the development of our product candidates, building our intellectual property portfolio, developing our supply chain, conducting business planning, raising capital and providing support for our operations. To date we have funded our operations through public and private placements of equity securities and upfront milestone payments. Through December 31, 2022, we have raised aggregate gross proceeds of \$401.8 million from private and public offerings, and we have received an aggregate of \$285.5 million in payments from our collaborators. Since our inception, we have incurred net losses and negative cash flows from our operations. Substantially all of our losses have resulted from funding our research and development programs and general and administrative costs associated with our operations. We incurred net losses of \$78.0 million, and \$68.3 million for the years ended December 31, 2022 and 2021, respectively. As of December 31, 2022 and 2021, we had an accumulated deficit of \$291.6 million and \$213.6 million, respectively. Our operating activities used \$68.7 million and \$44.6 million of cash outflows during the years ended December 31, 2022 and 2021, respectively.

We have not achieved profitability since our inception and we expect to continue to incur net losses for the foreseeable future.

We expect to fund our long-term anticipated operating and capital expenditure requirements through public and private offerings of our ADSs and ordinary shares.

Capital Requirements

In December 2021, we extended our facility lease for an additional five years through November 30, 2027. Under the terms of the lease, we are obligated to make aggregate remaining lease payments as of December 31, 2022, of \$14.7 million, excluding common area maintenance and other variable consideration due under the lease agreement. Estimated lease payments for the fiscal year ended December 31, 2023 are expected to be \$2.8 million, excluding common area maintenance and other variable consideration due under the lease agreement.

As of December 31, 2022, we have the following potential purchase obligations for which the timing and/or likelihood of occurrence is unknown; however, if such claims arise in the future, they could have a material effect on our financial position, results of operations, and cash flows.

- Under our license agreements and R&D Agreements, we have payment obligations, which are contingent upon future events such as our achievement of specified development, regulatory and commercial milestones and are required to make royalty payments in connection with the sales of products developed under those agreements. For additional details regarding these agreements, see the section titled “*Note 10—Revenues*” and *Note 7—Commitments and Contingencies* to our consolidated financial statements and related notes included elsewhere in this Annual Report;
- Obligations under contracts which are cancelable without significant penalty;
- Purchase orders issued in the ordinary course of business as they represent authorizations to purchase the items rather than binding agreements; and
- Contracts in the normal course of business with clinical supply manufactures and with vendors for preclinical studies, research supplies and other services and products for operating purposes. These contracts generally provide for termination after a notice period, and therefore are cancelable contracts and are not included in the table above.

Our future capital requirements will depend on many factors, including:

- the scope, progress, results and costs of drug discovery, preclinical development, laboratory testing and clinical trials for our product candidates;
- the costs, timing and outcome of regulatory review of our product candidates;
- the costs of establishing or contracting for sales, marketing and distribution capabilities if we obtain regulatory approvals to market our product candidates;
- the costs of securing and producing drug substance and drug product material for use in preclinical studies, clinical trials and for use as commercial supply;
- the costs of securing manufacturing arrangements for development activities and commercial production;
- the scope, prioritization and number of our research and development programs;
- the extent to which we are obligated to reimburse, or entitled to reimbursement of, clinical trial costs under future collaboration agreements, if any;
- the extent to which we acquire or in-license other product candidates and technologies; and
- the costs of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending intellectual property-related claims.

Our future capital requirements will depend on many factors, and we could use our available capital resources sooner than we currently expect. If our planned clinical trials and preclinical studies are successful, or other product candidates enter clinical trials or advance beyond the discovery stage, we will need to raise substantial additional financing in the future to fund our operations. In order to meet these additional cash requirements, we may incur debt, out-license certain intellectual property and seek to sell additional equity or convertible securities that may result in dilution to our shareholders. If we raise additional funds through the issuance of equity or convertible securities, these securities could have rights or preferences senior to those of our ADSs and ordinary shares and any indebtedness could contain covenants that restrict our operations. There can be no assurance that we will be able to obtain additional equity or debt financing on terms acceptable to us, if at all.

Cash Flows

The following table provides information regarding our cash flows for the years ended December 31, (in thousands):

	2022	2021
Operating activities	\$ (68,675)	\$ (44,640)
Investing activities	(46,718)	(3,206)
Financing activities	928	127,427
Effect of exchange rate changes on cash	—	47
Total (decrease) increase in cash and cash equivalents	<u>\$ (114,465)</u>	<u>\$ 79,628</u>

Net cash used in operating activities

During the year ended December 31, 2022, net cash used in operating activities of \$68.7 million consisted of a net loss of \$78.0 million, and \$10.6 million of cash used by net working capital changes, partially offset by \$19.9 million in adjustments for non-cash items. Overall, net cash used in operating activities was primarily related to the funding of our research and development activities, including preclinical and clinical program expenses, as well as supporting costs associated with general and administrative expenses. Adjustments for non-cash items primarily consisted of \$9.7 million of intangible asset impairments, \$6.3 million of share-based compensation expense, \$2.7 million of non-cash operating lease expense, \$1.1 million of intangible asset amortization, and \$0.8 million of depreciation of property and equipment, offset in part by \$0.5 million of accretion/amortization of investment securities, net. The decrease in net working capital consisted primarily of decreases related to deferred revenue of \$3.9 million, accrued liabilities of \$3.6 million, operating lease liabilities of \$2.1 million and accounts payable of \$1.8 million, offset in part by an increase of \$0.9 million related to accounts receivables.

During the year ended December 31, 2021, operating activities used \$44.6 million of cash, which was primarily attributable to our net loss of \$68.3 million, including net loss attributable to our redeemable noncontrolling interests of \$0.2 million, partially offset by noncash expenses of \$20.0 million and cash provided by changes in our operating assets and liabilities of \$3.6 million primarily related to the funding of our research and development activities, regulatory and other clinical trial costs for ARX788.

Net cash used in investing activities

During the year ended December 31, 2022, net cash used in investing activities consisted of \$84.9 million for purchases of MDS and \$1.1 million for the purchase of property and equipment to support our preclinical and clinical development activities, offset in part by cash inflows of \$37.0 million and \$2.2 million related to maturities and sales of MDS, respectively.

During the year ended December 31, 2021, uses of cash from investing activities consisted of \$2.0 million for the purchase of property and equipment to support our preclinical and clinical development activities and \$1.3 million for the purchase of a license agreement related to acquired technology.

Net cash provided by financing activities

During the year ended December 31, 2022, net cash provided by financing activities consisted of \$166.0 million related to borrowings of a short-term bridge loan, \$1.8 million of proceeds from our directors and officers premium financing agreement and \$0.1 million related to issuances of ordinary shares pursuant to our employee share purchase plan. These cash inflows were offset in part by cash outflows of \$166.0 million related to repayment of a short-term bridge loan, \$0.9 million for payments of our directors and officers premium financing agreement and \$0.1 million for settlement of ordinary shares issuance costs in accounts payable and accrued liabilities as of December 31, 2021.

During the year ended December 31, 2021, net cash provided by financing activities consisted of \$148.7 million of proceeds from issuances of ordinary shares, including issuance of ordinary shares in an initial public offering and upon underwriters' exercise of an overallotment option, and issuance of ordinary shares pursuant to share-based compensation plans. These cash inflows were partially offset by cash outflows of \$21.0 million to settle our redeemable noncontrolling interest and \$0.3 million for settlement of Series B preferred share issuance costs in accounts payable and accrued liabilities as of December 31, 2020.

Critical Accounting Policies and Significant Judgments and Estimates

Summarized below are our accounting policies that we believe are important to the portrayal of our financial results and also involve the need for management to make estimates about the effect of matters that are uncertain in nature. Actual results may differ from these estimates, judgments and assumptions. Certain accounting policies are particularly critical because of their significance to our reported financial results and the possibility that future events may differ significantly from the conditions and assumptions underlying the estimates used and judgments made by our management in preparing our financial statements. The following discussion should be read in conjunction with our consolidated financial statements and related notes.

Our consolidated financial statements are prepared in accordance with generally accepted accounting principles in the United States. The preparation of our consolidated financial statements and related disclosures requires us to make estimates, assumptions and judgments that affect the reported amount of assets, liabilities, revenue, costs and expenses, and related disclosures. We have identified certain accounting policies that are significant to the preparation of our consolidated financial statements. These accounting policies are important for an understanding of our financial condition and results of operations.

There have been no material changes from the significant accounting policies shown below and set forth in *Note 2—Summary of Significant Accounting Policies*, which include valuation of share-based awards, MDS, and other fair value measurements, the discount rate used in estimating the present value of the right-of-use (ROU) assets and lease liabilities, the useful lives of property and equipment and intangible assets, the recoverability of long-lived assets, clinical trial accruals, periods over which revenue should be recognized, deferred income taxes and related valuation allowances, and the assessment of the Company's ability to fund its operations for at least the next 12 months from the date of issuance of these consolidated financial statements.

Critical accounting policies are those most important to the portrayal of our financial condition and results of operations and require management's difficult, subjective, or complex judgment, often as a result of the need to make estimates about the effect of matters that are inherently uncertain and may change in subsequent periods. Certain accounting estimates are particularly sensitive because of their significance to financial statements and because of the possibility future events affecting the estimate may differ significantly from management's current judgments. We believe the following critical accounting policies involve the most significant estimates and judgments used in the preparation of our consolidated financial statements.

Impairment of Long-Lived Assets (Property and Equipment, and Intangible Assets)

In accordance with the authoritative guidance for impairment or disposal of long-lived assets ASC Topic 360, *Property, Plant and Equipment*, we assess potential impairments to our long-lived assets, including property, equipment and intangible assets, when there is evidence that events or changes in circumstances indicate that the carrying value may not be recoverable. We recognize an impairment loss when the undiscounted cash flows expected to be generated by an asset (or group of assets) are less than the asset's carrying value. Any required impairment loss would be measured as the amount by which the asset's carrying value exceeds its fair value and would be recorded as a reduction in the carrying value of the related asset and charged to results of operations.

In accordance with ASC Topic 350, *Intangibles—Goodwill and Other* (ASC 350), we test our acquired in-process research and development for impairment at least annually and more frequently if events or changes in circumstances indicate that it is more likely than not the asset is impaired. ASC 350 provides an unconditional option to bypass a qualitative assessment and only perform a quantitative impairment test at any time. Impairment losses, if any, would be recognized for the amount for which the carrying value exceeds the fair value of the asset. This amount would be recorded as a reduction in the carrying value of the related asset and charged to results of operations.

Assumptions and estimates used in evaluating our definite-lived assets future values and remaining useful lives are complex and often subjective. They can be affected by a variety of factors, including external factors such as industry and economic trends, and internal factors such as changes in our business strategy, internal forecasts and clinical trial results. For example, if we experience a sustained decline in our market capitalization determined to be indicative of a reduction in fair value of our enterprise, we may be required to record future impairment charges for our acquired technology intangible assets with finite lives. Impairment charges could materially decrease our future net income and result in lower asset values on our balance sheet.

If our indefinite-lived assets require a quantitative assessment to be performed, the evaluation would include management's estimates of cash flow projections based on internal future projections and/or use of a market approach by looking at market values of comparable companies. Key assumptions include, but are not limited to, future cash flows, operating margins, capital expenditures, terminal growth rates and discount rates. We also consider our market capitalization as a part of our analysis.

During the years ended December 31, 2022 and 2021, we recorded intangible asset impairment charges of \$9.7 million and \$0.5 million, respectively. For additional details regarding our intangible assets and related impairments see the sections titled *Intangible Assets, Net of Note2—Summary of Significant Accounting Policies* and *Note 4—Intangible Assets, Net*, to our consolidated financial statements and related notes included elsewhere in this Annual Report.

Clinical Trial Accruals

As part of the process of preparing our consolidated financial statements, we are required to estimate expenses resulting from our obligations under contracts with vendors, CROs, CMOs and consultants and under clinical site agreements relating to conducting our clinical trials. The financial terms of these contracts vary and may result in payment flows that do not match the periods over which materials or services are provided under such contracts.

Our objective is to reflect the appropriate clinical trial expenses in our consolidated financial statements by recording those expenses in the period in which services are performed and efforts are expended. We account for these expenses according to the progress of the clinical trial as measured by patient progression and the timing of various aspects of the trial. Management determines accrual estimates, as of each balance sheet date, through discussions with applicable personnel and outside service providers as to the progress of clinical trials.

During a clinical trial, we adjust the clinical expense recognition if actual results differ from estimates. We make estimates of accrued expenses as of each balance sheet date based on the facts and circumstances known at that time. Our clinical trial accruals are partially dependent upon accurate reporting by CROs and other third-party vendors. Although we do not expect estimates to differ materially from actual amounts, our understanding of the status and timing of services performed relative to the actual status and timing of services performed may vary and may result in reporting amounts that are too high or too low for any reporting period. For the years ended December 31, 2022 and 2021, there were no material adjustments to our prior period estimates of accrued expenses for clinical trials.

Marketable Debt Securities, Available-for-Sale

Our MDS portfolio, which is classified as available-for-sale, is comprised of money market funds, commercial paper, U.S. government securities, debt securities of U.S. financial institutions, corporate debt and asset backed securities. The objective of our investment policy is to preserve capital and maintain liquidity, with acceptable levels of risk. The investment policy limits interest-bearing security investments to certain types of debt and money market instruments issued by institutions with investment grade credit ratings, and it places restrictions on maturities and concentrations by asset class and issuer.

MDS are classified as either current or non-current assets in the consolidated balance sheets based on each instrument's underlying contractual maturity date. Generally, at the time of purchase, MDS with remaining maturities of greater than three months and less than 12 months are classified as current assets and MDS with remaining maturities greater than 12 months for which we have the intent and ability to hold the investment for greater than 12 months are classified as non-current assets. We may sell certain of our MDS prior to their stated maturities for strategic purposes or in anticipation of credit deterioration.

Our MDS are stated at fair value, with unrealized gains and losses, net of tax, if any, reported in accumulated other comprehensive loss in the consolidated balance sheets, until disposition or maturity. Dividend and interest income, amortization/accretion of premiums and discounts, and realized gains and losses, which are determined using the specific identification method, are recognized in investment income, net, in the consolidated statements of operations and comprehensive loss.

MDS are subject to a periodic impairment review. If we do not intend to sell and it is not more likely than not that we will be required to sell the security prior to recovery of its amortized cost basis, we will determine whether a decline in fair value below the amortized cost basis is due to credit-related factors. The credit loss is measured as the amount by which the debt security's amortized cost basis exceeds the estimate of the present value of cash flows expected to be collected, up to the difference between the amortized cost basis and the fair value. Impairment is assessed at the individual security level. Credit-related impairment is recognized as an allowance in the consolidated balance sheets with a corresponding adjustment to investment income, net, in the consolidated statements of operations and comprehensive loss. Any impairment that is not credit-related is recognized in accumulated other comprehensive loss in the consolidated balance sheets.

We do not separately measure an allowance for credit losses on accrued interest receivables on our MDS. We write off accrued interest receivables by reversing interest income in the period deemed uncollectible in investment income, net, in the consolidated statements of operations and comprehensive loss. Any accrued interest receivable on MDS is recorded in prepaid expenses and other current assets.

Revenue

We apply the five-step revenue recognition model within the scope of ASC Topic 606, *Revenue from Contracts with Customers* (ASC 606). Under this model, we: (i) identify the contract, (ii) identify the performance obligations in the contract, (iii) determine the transaction price, (iv) allocate the transaction price to the performance obligations in the contract, and (v) recognize revenue when, or as, a company satisfies a performance obligation. A performance obligation is a promise in a contract to transfer a distinct good or service and is the unit of accounting in ASC 606. A contract's transaction price is allocated among each distinct performance obligation based on relative standalone selling price and recognized as revenue when, or as, the applicable performance obligation is satisfied.

The terms of our R&D Agreements include upfront and license fees, R&D funding or reimbursements, milestone and other contingent payments for the achievement of defined objectives and certain preclinical, clinical, regulatory and sales-based events, as well as royalties on sales of commercialized products. Agreements with certain upfront payments may require deferral of revenue recognition to a future period until we perform the obligations under these agreements. We use the most likely amount method to estimate variable consideration for event-based milestones and other contingent payments. Given the high degree of uncertainty around the occurrence of such events, the event-based milestones and other contingent payments have been fully constrained until any uncertainty associated with these payments is resolved. Revenue from sales-based milestones and royalty payments is recognized at the later of when or as the sales occur or when the related performance obligation has been satisfied or partially satisfied. We continue to re-evaluate the transaction price in each reporting period as contingencies are resolved and other changes in circumstances occur.

Revenue recognition is subject to uncertainty due to the variable consideration estimates required to be made. These estimates include the level of effort required to satisfy our obligations under our R&D services arrangements. These amounts are estimated at the inception of an R&D services arrangement and are re-evaluated at each reporting period. To accomplish this, we rely on management's experience, relevant internal data reports and regulatory approvals. The recorded variable consideration is directly sensitive to the estimated inputs made by management used in the calculation. Changes in estimates are accounted for prospectively.

During the second half of 2021, we re-evaluated our level of effort expected to be incurred for one of our licensed preclinical candidates which resulted in a cumulative effect catch-up adjustment to revenue, therefore reducing revenue recognized by approximately \$1.4 million. A hypothetical 10% increase/decrease in the estimated level of effort under this R&D services arrangement, would have resulted in a decrease/increase of approximately \$0.1 million in the cumulative catch-up adjustment recognized during the year ended December 31, 2021. Due to the BeiGene Notification (see Note 10—*Revenues*) during the fourth quarter of 2022, we re-evaluated our level of effort expected to be incurred for one of our licensed preclinical candidates which resulted in us accelerating approximately \$0.4 million in revenue previously expected to be recognized during the first quarter of 2023.

Item 7A. Quantitative and Qualitative Disclosures About Market Risk.

We are exposed to market risks from interest rates and foreign exchange rates.

Interest Rate

We are exposed to market risk primarily related to changes in interest rates. As of December 31, 2022, our cash and cash equivalents consisted of cash, commercial paper, certificates of deposit and money market funds, and our investments consisted of commercial paper, U.S. government securities, certificates of deposit, corporate bonds, asset backed securities and non-U.S. government securities with maturities up to 2.1 years as of December 31, 2022. As of December 31, 2022, we had cash, cash equivalents and marketable debt securities, available-for-sale, or MDS, of \$101.3 million, of which \$16.8 million are non-current MDS. Because of the relatively short-term nature and low risk profile of the instruments in our portfolio, a 100 basis point increase or decrease in market interest rates would not have a material impact on our financial condition or results of operations for any periods presented herein.

Foreign Currencies

Our consolidated financial statements include the financial statements of our subsidiary in China, which through June 30, 2021, were denominated in Renminbi and, therefore, we were exposed to risks related to movements between the Renminbi and the U.S. dollar. Given our expenditures in Renminbi account for less than 2.0% of our total operating expenses, to date, we have not used any derivative financial instruments to hedge exposure to foreign exchange risk. We do not currently have any significant direct foreign exchange risk. We expect our expenditures and funding sources will continue to be primarily denominated in the U.S. dollar. However, depending on our partner's product sales in China in the future, our Renminbi exposure may increase in the future.

The value of the Renminbi against the U.S. dollar and other currencies may fluctuate and is affected by, among other things, changes in political and economic conditions in China and by China's foreign exchange policies. It is difficult to predict how market forces may impact the exchange rate between the Renminbi and the U.S. dollar. To the extent that we need to convert U.S. dollars into Renminbi for our operations, appreciation of the Renminbi against the U.S. dollar could have an adverse effect on the Renminbi amount we receive from the conversion.

We also contract with vendors that are located outside of the United States and certain invoices are denominated in Euros, Australian dollars and Swiss Francs. We are subject to fluctuations in foreign currency rates in connection with these arrangements. We do not currently hedge our foreign currency exchange rate risk. As of December 31, 2022, we had minimal or no liabilities denominated in Euros, Australian dollars and Swiss Francs.

Inflation Risk

We are subject to inflationary pressures with respect to labor and other costs. In this regard, inflation rates in the United States increased significantly during the year ended December 31, 2022. We do not believe that inflation has had a material effect on our financial condition or results of operations for any periods presented herein. However, there is a risk that our operating costs may become subject to inflationary pressure in the future, which would put additional stress on our working capital resources.

Item 8. Financial Statements and Supplementary Data.

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REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

To the shareholders and the Board of Directors of Ambrx Biopharma Inc.

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of Ambrx Biopharma Inc. and subsidiaries (the "Company") as of December 31, 2022 and 2021, the related consolidated statements of operations and comprehensive loss, changes in redeemable noncontrolling interests, convertible preferred shares and shareholders' equity (deficit), and cash flows for each of the two years in the period ended December 31, 2022, and the related notes (collectively referred to as the "financial statements"). In our opinion, the financial statements present fairly, in all material respects, the financial position of the Company as of December 31, 2022 and 2021, and the results of its operations and its cash flows for each of the two years in the period ended December 31, 2022, in conformity with accounting principles generally accepted in the United States of America.

Basis for Opinion

These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on the Company's financial statements based on our audits. We are a public accounting firm registered with the Public Company Accounting Oversight Board (United States) (PCAOB) and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement, whether due to error or fraud. The Company is not required to have, nor were we engaged to perform, an audit of its internal control over financial reporting. As part of our audits, we are required to obtain an understanding of internal control over financial reporting but not for the purpose of expressing an opinion on the effectiveness of the Company's internal control over financial reporting. Accordingly, we express no such opinion.

Our audits included performing procedures to assess the risks of material misstatement of the financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the financial statements. We believe that our audits provide a reasonable basis for our opinion.

/s/ Deloitte & Touche LLP

San Diego, California
March 30, 2023

We have served as the Company's auditor since 2020.

AMBRX BIOPHARMA INC.**CONSOLIDATED BALANCE SHEETS****(in thousands of USD, except share and per share data)**

	December 31, 2022	December 31, 2021
ASSETS		
Current assets:		
Cash and cash equivalents	\$ 55,610	\$ 170,064
Restricted Cash	831	842
Marketable debt securities, available-for-sale	28,873	—
Accounts receivable, net	376	1,239
Prepaid expenses and other current assets	4,893	4,661
Total current assets	90,583	176,806
Marketable debt securities, available-for-sale, net of current portion	16,793	—
Property and equipment, net	3,044	2,984
Right-of-use assets, net	10,968	12,737
Intangible assets, net	25,250	35,962
Other long-term assets	339	530
Total assets	<u>\$ 146,977</u>	<u>\$ 229,019</u>
LIABILITIES AND SHAREHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	\$ 3,205	\$ 5,272
Accrued liabilities	11,314	14,125
Operating lease liabilities, current portion	1,734	915
Deferred revenue, current portion	407	4,267
Total current liabilities	16,660	24,579
Operating lease liabilities, net of current portion	10,245	12,212
Deferred tax liabilities	880	880
Deferred revenue, net of current portion	1,342	1,381
Total liabilities	29,127	39,052
Commitments and contingencies (Note 7)		
SHAREHOLDERS' EQUITY		
Ordinary Shares, par value \$0.0001; 500,000,000 shares authorized at December 31, 2022 and 2021; 270,455,232 and 270,120,548 shares issued and outstanding as of December 31, 2022 and 2021, respectively	27	27
Additional paid-in capital	410,753	404,362
Accumulated other comprehensive loss	(1,302)	(790)
Accumulated deficit	(291,628)	(213,632)
Total shareholders' equity	117,850	189,967
Total liabilities and shareholders' equity	<u>\$ 146,977</u>	<u>\$ 229,019</u>

The accompanying notes are an integral part of these consolidated financial statements.

AMBRX BIOPHARMA INC.
CONSOLIDATED STATEMENTS OF OPERATIONS AND COMPREHENSIVE LOSS
(in thousands of USD, except share and per share data)

	Years ended December 31,	
	2022	2021
Revenues	\$ 7,402	\$ 7,455
Operating expenses:		
Research and development	53,307	54,295
General and administrative	20,836	17,071
Impairment of intangible assets	9,660	513
Total operating expenses	83,803	71,879
Loss from operations	(76,401)	(64,424)
Other income (expense), net:		
Investment income, net	1,337	—
Interest expense, net	(968)	—
Other (expense) income, net	(27)	40
Change in fair value of redeemable noncontrolling interests	—	(3,903)
Total other income (expense), net	342	(3,863)
Loss before income taxes	(76,059)	(68,287)
Provision for income taxes	(1,937)	(1)
Net loss	(77,996)	(68,288)
Less: Net loss attributable to the redeemable noncontrolling interests	—	209
Net loss attributable to Ambrx Biopharma Inc. shareholders	\$ (77,996)	\$ (68,079)
Net loss per share applicable to Ambrx Biopharma Inc. ordinary shareholders—basic and diluted	\$ (0.29)	\$ (0.48)
Weighted-average ordinary shares used to compute net loss per share attributable to ordinary shareholders—basic and diluted	270,241,698	143,175,224
Other comprehensive loss, net of tax:		
Net loss	\$ (77,996)	\$ (68,288)
Other comprehensive loss, net of tax:		
Foreign currency translation adjustments	—	(18)
Unrealized losses on marketable debt securities, available-for-sale	(512)	—
Total other comprehensive loss	(512)	(18)
Comprehensive loss	(78,508)	(68,306)
Less: Comprehensive loss attributable to the redeemable noncontrolling interests	—	208
Comprehensive loss attributable to Ambrx Biopharma Inc.	\$ (78,508)	\$ (68,098)

The accompanying notes are an integral part of these consolidated financial statements.

AMBRX BIOPHARMA INC.

CONSOLIDATED STATEMENTS OF CHANGES IN REDEEMABLE NONCONTROLLING INTERESTS, CONVERTIBLE PREFERRED SHARES AND SHAREHOLDERS' (DEFICIT) EQUITY
(in thousands of USD, except share data)

	Redeemable Noncontrolling Interests	Series A Preferred Shares	Series B Preferred Shares	Ordinary Shares	Additional Paid-in Capital	Accumulated Other Comprehensive Loss	Accumulated Deficit	Total
	Shares	Amount	Shares	Par Value				
Balance as of December 31, 2020	\$ 1,287	\$ 135,936,550	\$ 57,575,008	\$ —	\$ 6,805	\$ (686)	\$ —	\$ (139,434)
Share-based compensation	—	—	—	—	11,856	—	—	11,856
Conversion of preferred stock into ordinary shares upon closing of initial public offering	—	—	—	19	253,012	—	—	253,031
Issuance of ordinary shares in an initial public offering for cash	—	—	—	5	113,149	—	—	113,154
Issuance of ordinary shares upon exercise of over-allotment option	—	—	—	1	14,946	—	—	14,947
Issuance of ordinary shares for cash	—	—	—	2	20,493	—	—	20,495
Accretion of redeemable noncontrolling interests to fair value of redeemable noncontrolling interests	42,324	—	—	—	(42,324)	—	—	(42,324)
Settle of redeemable noncontrolling interest	—	—	—	—	85	(85)	—	—
Reclassify NCI to current liability	(43,403)	—	—	—	—	—	—	—
Reclassify freestanding forward sale contract upon settlement of redeemable noncontrolling interests	—	—	—	—	26,340	—	—	26,340
Foreign currency translation adjustments	1	—	—	—	—	(19)	—	(19)
Net loss	(209)	—	—	—	—	—	(68,079)	(68,079)
Balance as of December 31, 2021	—	—	—	27	404,362	(790)	(213,632)	189,967
Share-based compensation	—	—	—	—	6,253	—	—	6,253
Issuance of ordinary shares for cash	—	—	—	—	138	—	—	138
Unrealized loss on marketable debt securities available-for-sale	—	—	—	—	—	—	—	—
Net loss	—	—	—	—	—	(512)	—	(512)
Balance as of December 31, 2022	\$ —	\$ —	\$ —	\$ 27	\$ 410,753	\$ (1,302)	\$ (291,628)	\$ 117,850

The accompanying notes are an integral part of these consolidated financial statements.

AMBRX BIOPHARMA INC.

CONSOLIDATED STATEMENTS OF CASH FLOWS
(in thousands of USD)

	Year ended December 31,	
	2022	2021
Cash flows from operating activities:		
Net loss	\$ (77,996)	\$ (68,288)
Noncash adjustments reconciling net loss to cash flows from operating activities:		
Loss on impairment of intangible assets	9,660	513
Share-based compensation expense	6,253	11,856
Noncash lease expense	2,730	1,582
Amortization of intangible assets	1,052	1,604
Depreciation and amortization	751	550
Loss on disposal of property and equipment	6	—
Accretion/amortization of investment securities, net	(510)	—
Change in fair value of redeemable noncontrolling interests	—	3,903
Changes in operating assets and liabilities:		
Accounts receivable, net	863	(811)
Prepaid and other current assets and other long-term assets	(41)	(2,629)
Accounts payable	(1,829)	2,403
Accrued liabilities	(3,605)	10,502
Deferred revenue	(3,899)	(4,083)
Operating lease liabilities	(2,110)	(1,742)
Net cash used in operating activities	(68,675)	(44,640)
Cash flows from investing activities:		
Purchases of marketable debt securities, available-for-sale	(84,852)	—
Sales of marketable debt securities, available-for-sale	2,188	—
Maturities of marketable debt securities, available-for-sale	37,000	—
Purchases of property and equipment	(1,054)	(1,956)
Acquisition of intangible assets	—	(1,250)
Net cash used in investing activities	(46,718)	(3,206)

The accompanying notes are an integral part of these consolidated financial statements.

AMBRX BIOPHARMA INC.
CONSOLIDATED STATEMENTS OF CASH FLOWS — (Continued)
(in thousands of USD)

	Year ended December 31,	
	2022	2021
Cash flows from financing activities:		
Proceeds from short-term bridge loan	166,000	—
Repayment of short-term bridge loan	(166,000)	—
Proceeds from directors and officers insurance premium financing agreement	1,831	—
Payments of directors and officers insurance premium financing agreement	(905)	—
Proceeds from issuance of ordinary shares, net of issuance costs	138	148,732
Payments to acquire the Ambrx Shanghai noncontrolling interests	—	(20,966)
Payments of costs for the issuance of Series B preferred shares	—	(339)
Payments of costs for the issuance of ordinary shares	(136)	—
Net cash provided by financing activities	928	127,427
Effect of exchange rate changes on cash, cash equivalents and restricted cash	—	47
Net (decrease) increase in cash, cash equivalents and restricted cash	(114,465)	79,628
Cash, cash equivalents and restricted cash, beginning of period	170,906	91,278
Cash, cash equivalents and restricted cash, end of period	<u>\$ 56,441</u>	<u>\$ 170,906</u>
Supplemental information:		
Cash paid for interest	<u>\$ 963</u>	<u>\$ —</u>
Cash paid for income taxes	<u>\$ 319</u>	<u>\$ 1</u>
Noncash investment and financing activities:		
Property and equipment costs in accounts payable and accrued liabilities	<u>\$ 491</u>	<u>\$ 727</u>
ROU assets and lease liabilities obtain through reassessment of an existing lease	<u>\$ —</u>	<u>\$ 11,455</u>
Conversion of convertible preferred shares into ordinary shares	<u>\$ —</u>	<u>\$ 253,031</u>
Reclassification of redeemable noncontrolling interests from temporary equity to current liabilities	<u>\$ —</u>	<u>\$ 43,403</u>
Accretion of redeemable noncontrolling interests to fair value	<u>\$ —</u>	<u>\$ 42,324</u>
Deferred initial public offering costs in accounts payable and accrued liabilities	<u>\$ —</u>	<u>\$ 136</u>
Reclassification of accumulated other comprehensive loss upon settlement of redeemable noncontrolling interests	<u>\$ —</u>	<u>\$ 85</u>

The accompanying notes are an integral part of these consolidated financial statements.

1. Description of Business and Basis of Presentation

Description of Business

Ambrx Biopharma Inc. (Ambrx or the Company) is a clinical-stage biologics company focused on discovering and developing a novel class of engineered precision biologics using its proprietary expanded genetic code technology platform that allows it to incorporate, in a site-specific manner, synthetic amino acids into proteins within living cells.

Ambrx commenced its operations in the United States in January 2003 when Ambrx Inc. (Ambrx US), was incorporated in Delaware. In May 2015, Ambrx incorporated under the laws of the Cayman Islands and has become the ultimate holding company (Ambrx Cayman) through a series of transactions. As of the date of these consolidated financial statements, the Company owned 100% of Shanghai Ambrx Biopharma Company Limited (Ambrx Shanghai) (see Reorganization discussion below) and Biolaxy Pharmaceutical Hong Kong Limited, a company incorporated in Hong Kong (Ambrx HK). Ambrx HK owned 100% of Ambrx US, and Ambrx US owned 100% of Ambrx Australia Pty Limited, a company incorporated in Australia (Ambrx AU). Ambrx US is based in San Diego, California.

Prior to Ambrx Shanghai becoming a wholly owned subsidiary (see Reorganization discussion below), the Company had recognized redeemable noncontrolling interests in its consolidated financial statements for the 11% it did not directly own. As of June 30, 2021, the Company no longer recognizes redeemable noncontrolling interests in its consolidated financial statements.

Reorganization

During the second quarter of 2021, the Company completed a reorganization of its corporate structure (the Reorganization). The Reorganization primarily related to the Company's redeemable noncontrolling interests (RNCI), which represented the approximately 11% equity interest in the Company's subsidiary, Ambrx Shanghai, that was not attributable, either directly or indirectly, to the Company, and was recognized separately from the Company's controlling interest within its consolidated financial statements.

In April 2021, the Company purchased all outstanding shares of Ambrx HK from Ambrx Shanghai for an aggregate purchase price of \$190.0 million, through the issuance of a promissory note to Ambrx Shanghai by Ambrx for the purchase price. As a result of these common control transactions, Ambrx Shanghai and Ambrx HK both became wholly owned subsidiaries of Ambrx in April 2021. This promissory note was settled in the first quarter of 2022, through the payment of \$24.0 million in cash by Ambrx to Ambrx Shanghai and a capital reduction in Ambrx Shanghai of \$166.0 million (the Capital Reduction). To effect the Capital Reduction in Ambrx Shanghai and to comply with regulatory requirements in the People's Republic of China, the Company borrowed \$166.0 million in the form of a short-term bridge loan from a financial institution incurring approximately \$1.0 million in fees and interest and repaid the loan with the proceeds from the Capital Reduction.

In connection with the Reorganization, the Company and the approximately 11% minority shareholders of Ambrx Shanghai (the Shanghai Shareholders) signed the Reorganization agreements dated March 23, 2021, as amended in April 2021. During the second quarter of 2021, in accordance with the Reorganization agreements, the Company (a) paid the Shanghai Shareholders an aggregate of approximately \$21.0 million for the purchase of the RNCI, and (b) sold to certain of the Shanghai Shareholders an aggregate of 2,004,879 ordinary shares for aggregate gross proceeds of approximately \$2.1 million.

Prior to the execution of the Reorganization agreements, the Company's RNCI was classified outside of permanent equity because, upon certain contingent events that were not solely within the Company's control, it may have been required to purchase the RNCI. Through December 31, 2020, the Company did not adjust the carrying value of the RNCI to its redemption value since a certain contingent event was not probable of occurrence. Through March 31, 2021, revenues, expenses, gains, losses, net loss and other comprehensive loss were reported in the financial statements at the consolidated amounts, which included the amounts attributable to both the controlling and redeemable noncontrolling interests.

Upon execution of the Reorganization agreements, the Company's RNCI became mandatorily redeemable as the Company became contractually obligated to purchase the RNCI. Therefore, the Company reclassified the RNCI from outside of permanent equity to a current liability upon which the RNCI was no longer subject to allocation of losses or other comprehensive losses. The Company identified two forward contracts embedded within the RNCI (the Forward Contracts). The first forward contract is the forward purchase contract for the Company to purchase all the RNCI from the Shanghai Shareholders for a fixed price of \$36.7 million (the Forward Purchase Contract), and the second forward contract is the forward sale contract for the Company to sell a fixed number of ordinary shares to the Shanghai Shareholders for a fixed price of \$36.0 million (the Forward Sale Contract).

The Forward Contracts were determined to be embedded in the Company's RNCI (the Combined RNCI). Upon the execution of the Reorganization agreements, the Combined RNCI was reclassified from temporary equity to a current liability at fair value of \$43.4 million in the Company's consolidated balance sheets. The initial fair value of the Combined RNCI was determined using level three inputs of the fair value hierarchy including equity value of the Company determined using combinations of income and market approaches and estimated expiration term. Subsequent changes in fair value of the Combined RNCI were recorded as a component of other income (expense), net, in the consolidated statements of operations and comprehensive loss until the liability was fully settled in June 2021.

In April 2021, the Company and the Shanghai Shareholders amended the Reorganization agreements to reduce the purchase price of both the Forward Purchase Contract and the Forward Sale Contract by \$15.7 million (the Amendment). The Amendment resulted in a \$0.3 million decrease in the fair value of the Combined RNCI liability.

During the year ended December 31, 2021, the Company recorded a \$3.9 million loss due to a changes in fair value associated with the Combined RNCI. Upon the \$21.0 million cash settlement of the RNCI during the second quarter of 2021, the Forward Sale Contract was determined to meet the scope exception in ASC 815-10 – *Derivatives and Hedging* for equity classification and was determined to be an equity classified freestanding financial instrument in accordance with ASC Topic 480, *Distinguishing Liabilities from Equity*. Accordingly, the Company reclassified the fair value associated with the Forward Sale Contract of \$26.3 million to additional paid-in-capital in the consolidated balance sheets.

Initial Public Offering

In June 2021, the Company completed its initial public offering (the IPO) of 7,000,000 American Depositary Shares (ADSs) at an offering price of \$18.00 per ADS. Each ADS represents seven ordinary shares of the Company. Net proceeds from the IPO were approximately \$113.2 million, net of underwriting discounts and commissions of \$8.8 million and offering-related transaction costs, including direct legal, accounting and other professional fees incurred of approximately \$4.0 million. In connection with the IPO, the Company's outstanding convertible preferred shares were automatically converted into 193,511,558 ordinary shares and were reclassified into permanent shareholders' equity. Following the IPO, there were no convertible preferred shares outstanding.

In July 2021, the underwriters exercised their overallotment option to purchase 892,831 ADSs at the initial offering price of \$18.00 per ADS for net proceeds to the Company of \$14.9 million after underwriting discounts and commissions.

Basis of Presentation and Principles of Consolidation

The accompanying consolidated financial statements have been prepared in accordance with accounting principles generally accepted in the United States of America (U.S. GAAP). The Company's consolidated financial statements include the accounts of the Company and its wholly owned subsidiaries. Intercompany accounts and transactions have been eliminated in consolidation. The Company's operating currency is the U.S. dollar. Prior to June 30, 2021, in general, the functional currency of the Company's subsidiaries was the U.S. dollar; however, for Ambrx Shanghai the functional currency was the local currency. Consequently, through June 30, 2021, assets and liabilities for Ambrx Shanghai were translated into U.S. dollars, and the effects of foreign currency translation adjustments were included as a component of accumulated other comprehensive loss within the Company's consolidated statements of changes in redeemable noncontrolling interests, convertible preferred shares and

shareholders' (deficit) equity. Effective July 1, 2021, the functional currency for all the Company's subsidiaries is the U.S. dollar. As such, the Company no longer recognizes currency translation adjustments as a component of accumulated other comprehensive loss, rather all adjustments are recorded in other income (expense), net, in the consolidated statements of operations and comprehensive loss.

Liquidity and Capital Resources

The Company has incurred net operating losses and negative cash flows from operations since its incorporation in 2015 and had an accumulated deficit of \$291.6 million as of December 31, 2022. As of December 31, 2022, the Company had cash, cash equivalents and marketable debt securities, available-for-sale (MDS) of \$101.3 million, of which \$16.8 million are non-current MDS. Management believes its existing financial resources are sufficient to continue operating activities for at least 12 months past the issuance date of these consolidated financial statements. Future capital requirements will depend on many factors, including the timing and extent of spending on research and development (R&D) activities and market acceptance of the Company's products, if approved.

Until such time the Company can generate significant revenue from product sales, if ever, the Company expects to finance its operations through public or private equity or debt financings or other capital sources, which may include strategic collaborations or other arrangements with third parties. However, the Company may be unable to raise additional funds or enter into such other agreements or arrangements when needed on favorable terms, or at all. If the Company is unable to raise capital or enter into such agreements as and when needed, the Company may have to significantly delay, scale back or discontinue the development or commercialization of one or more of its product candidates. Insufficient liquidity may also require the Company to relinquish rights to product candidates at an earlier stage of development or on less favorable terms than the Company would otherwise choose. The Company's ability to raise additional funds may be adversely impacted by potential worsening global macroeconomic and geopolitical conditions and disruptions to, and volatility in, the credit and financial markets in the United States and worldwide, including from the ongoing COVID-19 pandemic and related variants, the ongoing conflict between Ukraine and Russia and recent disruption in access to bank deposits and lending commitments due to bank failures.

2. Summary of Significant Accounting Policies

Use of Estimates

The preparation of consolidated financial statements in conformity with U.S. GAAP requires management to make estimates and assumptions that affect the amounts of assets and liabilities and disclosure of contingent assets and liabilities at the date of the consolidated financial statements and the reported amounts of revenues and expenses during the reporting period. On an ongoing basis, the Company evaluates its estimates, including those related to the valuation of share-based awards, MDS, and other fair value measurements, the discount rate used in estimating the present value of the right-of-use (ROU) assets and lease liabilities, the useful lives of property and equipment and intangible assets, the recoverability of long-lived assets, clinical trial accruals, periods over which revenue should be recognized, deferred income taxes and related valuation allowances, and the assessment of the Company's ability to fund its operations for at least the next 12 months from the date of issuance of these consolidated financial statements. The Company bases its estimates on historical experience and other market-specific or other relevant assumptions that it believes to be reasonable under the circumstances. Estimates are assessed each reporting period and updated to reflect current information. As future events and their effects cannot be determined with precision, actual results may materially differ from those estimates or assumptions.

Due to the recent disruption in access to bank deposits and lending commitments due to bank failures, the COVID-19 pandemic and macroeconomic and geopolitical conditions, there has been uncertainty and disruption in the global economy and financial markets. The Company is not aware of any specific event or circumstance that would require an update to its estimates or judgments or a revision of the carrying value of its assets or liabilities as of December 31, 2022. While there was no material impact to the Company's consolidated financial statements as of and for the year ended December 31, 2022, these estimates may change, as new events occur and additional information is obtained, which could materially impact the Company's consolidated financial statements in future reporting periods.

Segment Reporting

Operating segments are identified as components of an enterprise about which separate discrete financial information is available for evaluation by the chief operating decision-maker, who is the Chief Executive Officer of the Company, in making decisions regarding resource allocation and assessing performance. The Company views its operations and manages its business in one operating segment.

Risk and Uncertainties

Since December 2019, COVID-19, a novel strain of coronavirus has become a global pandemic. The virus continues to spread globally, has been declared a pandemic by the World Health Organization and has spread to over 100 countries, including the United States. The impact of this pandemic has been and will likely continue to be extensive in many aspects of society, which has resulted in and will likely continue to result in significant disruptions to the global economy, as well as businesses and capital markets around the world.

The full extent to which the COVID-19 pandemic will directly or indirectly impact the Company's business, results of operations and financial condition, including expenses, clinical trials and other costs, will depend on future developments that are highly uncertain, including as a result of new information that may emerge concerning COVID-19 and the actions taken to contain or treat COVID-19, as well as the economic impact on local, regional, national and international markets.

Concentrations of Credit Risk

Financial instruments that potentially subject the Company to significant concentrations of credit risk consist primarily of cash and cash equivalents, restricted cash, MDS, and accounts receivable which are generally not collateralized. Deposits in the Company's checking and money market accounts are maintained in federally insured financial institutions and are subject to federally insured limits or limits set by the Securities Investor Protection Corporation. In addition, the Company maintains cash and cash equivalents in foreign bank accounts, which are not federally insured.

The Company attempts to minimize credit risk associated with its cash and cash equivalents by periodically evaluating the credit quality of its primary financial institutions. The Company's investment portfolio is maintained in accordance with its investment policy, which is designed to preserve capital, safeguard funds and limit exposure to risk. While the Company maintains cash deposits in FDIC insured financial institutions in excess of federally insured limits, it does not believe that it is exposed to significant credit risk due to the financial position of the depository institutions in which those deposits are held. The Company has not experienced any losses on such accounts.

During the year ended December 31, 2022, revenues from the Company's top two customers represented 65.9% and 25.6% of total revenues, respectively. During the year ended December 31, 2021, revenues from the Company's top two customers represented 56.8% and 35.8% of total revenues, respectively.

As of December 31, 2022, billed accounts receivable for two customers represented 78.4% and 11.8% of total billed receivables, respectively. As of December 31, 2021, billed accounts receivable for two customers represented 74.6% and 21.3% of total billed receivables, respectively.

Cash, Cash Equivalents and Restricted Cash

Cash and cash equivalents consist of readily available cash in checking accounts, money market funds and other MDS with original maturities of three months or less.

The following table provides a reconciliation of cash, cash equivalents and restricted cash, reported within the consolidated statements of cash flows for the years ended December 31, (in thousands):

	2022	2021
Cash and cash equivalents	\$ 55,610	\$ 170,064
Restricted cash	831	842
Total cash, cash equivalents, and restricted cash presented in the consolidated statements of cash flows	<u>\$ 56,441</u>	<u>\$ 170,906</u>

As of December 31, 2022 and 2021, the Company's restricted cash consists of cash related to the Company's clinical trials.

Accounts Receivable, Net

Accounts receivable, net, are recorded net of any allowance for current expected credit losses measured based on historical experience, current conditions, and reasonable and supportable forecasts. As of December 31, 2022 and 2021, the Company has determined an allowance for expected credit losses is not material.

Contract Balances

The timing of revenue recognition, billings and cash collections results in billed accounts receivable, unbilled receivables (contract assets) and deferred revenue (contract liabilities) on the consolidated balance sheet, recorded on a contract-by-contract basis at the end of each reporting period.

The majority of the Company's contract amounts are invoiced as work progresses in accordance with agreed-upon contractual terms, either at periodic intervals or upon achievement of contractual milestones. Billing sometimes occurs subsequent to revenue recognition, resulting in contract assets. These contract assets are referred to as unbilled receivables and are reported within prepaid expenses and other current assets on the consolidated balance sheets. Unbilled receivables are transferred to accounts receivables, net, when the Company's right of receipt becomes unconditional.

Contract liabilities from the Company's R&D agreements (R&D Agreements) arise when amounts invoiced to customers exceed revenues recognized based upon measure of progress achieved. Contract liabilities additionally include advanced payments from customers on certain contracts. Contract liabilities decrease as the Company recognizes revenue from the satisfaction of the related performance obligation. Contract liabilities are included in deferred revenue, current portion and deferred revenue, net of current portion, on the consolidated balance sheets.

Marketable Debt Securities, Available-for-Sale

The Company's MDS portfolio, which is classified as available-for-sale, is comprised of money market funds, commercial paper, U.S. government securities, debt securities of U.S. financial institutions, corporate debt and asset backed securities. The objective of the Company's investment policy is to preserve capital and maintain liquidity, with acceptable levels of risk. The investment policy limits interest-bearing security investments to certain types of debt and money market instruments issued by institutions with investment grade credit ratings, and it places restrictions on maturities and concentrations by asset class and issuer.

MDS are classified as either current or non-current assets in the consolidated balance sheets based on each instrument's underlying contractual maturity date. Generally, at the time of purchase, MDS with remaining maturities of greater than three months and less than 12 months are classified as current assets and MDS with remaining maturities greater than 12 months for which the Company has the intent and ability to hold the investment for greater than 12 months are classified as non-current assets. The Company may sell certain of its MDS prior to their stated maturities for strategic purposes or in anticipation of credit deterioration.

The Company's MDS are stated at fair value, with unrealized gains and losses, net of tax, if any, reported in accumulated other comprehensive loss in the consolidated balance sheets, until disposition or maturity. Dividend and interest income, amortization/accretion of premiums and discounts, and realized gains and losses, which are determined using the specific identification method, are recognized in investment income, net, in the consolidated statements of operations and comprehensive loss.

MDS are subject to a periodic impairment review. If the Company does not intend to sell and it is not more likely than not that it will be required to sell the security prior to recovery of its amortized cost basis, the Company will determine whether a decline in fair value below the amortized cost basis is due to credit-related factors. The credit loss is measured as the amount by which the debt security's amortized cost basis exceeds the estimate of the present value of cash flows expected to be collected, up to the difference between the amortized cost basis and the fair value. Impairment is assessed at the individual security level. Credit-related impairment is recognized as an allowance in the consolidated balance sheets with a corresponding adjustment to investment income, net, in the consolidated statements of operations and comprehensive loss. Any impairment that is not credit-related is recognized in accumulated other comprehensive loss in the consolidated balance sheets.

The Company does not separately measure an allowance for credit losses on accrued interest receivables on its MDS. The Company writes off accrued interest receivables by reversing interest income in the period deemed uncollectible in investment income, net, in the Company's consolidated statements of operations and comprehensive loss. Any accrued interest receivable on MDS is recorded in prepaid expenses and other current assets in the consolidated balance sheets.

Property and Equipment, Net

Property and equipment is recorded at cost and depreciated over the estimated useful lives of the assets using the straight-line method. Leasehold improvements are stated at cost and are amortized on a straight-line basis over the lesser of the remaining term of the related lease or the estimated useful lives of the assets. Repairs and maintenance costs are charged to expense as incurred and improvements and betterments are capitalized.

Depreciation is calculated over their estimated useful lives as follows:

Laboratory equipment	5 years
Computer, software and office equipment	3 - 8 years
Furniture and fixtures	5 years

The useful lives of the Company's assets are reviewed annually. When assets are retired or otherwise disposed of, the cost and accumulated depreciation are removed from the consolidated balance sheets and any resulting gain or loss is reflected in the consolidated statements of operations and comprehensive loss in the period realized.

Intangible Assets, Net

The Company records its intangible assets based on their fair values at the date of acquisition. The Company's finite lived intangible assets related to acquired technologies has estimated remaining useful lives between three to 12 years as of December 31, 2022, and four to 13 years as of December 31, 2021. Amortization expense for the Company's finite lived intangible assets is charged to research and development expense in the consolidated statements of operations and comprehensive loss on a straight-line basis over the assets' estimated useful lives.

Impairment losses on finite-lived intangible assets are recorded when indicators of impairment are present and the undiscounted cash flows estimated to be generated by those assets are less than the assets' carrying amount. If such assets are considered impaired, the impairment to be recognized is measured by the amount by which the carrying amount of the assets exceeds the estimated fair value of the assets. During the fourth quarter of 2021, the Company determined the estimated undiscounted future cash flows of one of its acquired technology intangible assets was less than its carrying value and therefore recorded an impairment charge of \$0.5 million.

In the first quarter of 2022, the Company received a Notice of Termination of Collaboration and License agreement (Relaxin) between Bristol-Myers Squibb Company (BMS) and the Company (the Relaxin Agreement) from BMS to be effective three months from receipt of the notification. Due to this termination notice and the Company's determination that the asset had no alternative future use, the Company concluded the net carrying value of the BMS Relaxin intangible asset was greater than its estimated fair value and therefore recorded an impairment charge of \$2.5 million.

In the second quarter of 2022, the Company received verbal notification from BMS of its intent to terminate the Collaboration and License Agreement (FGF-21) between BMS and the Company (the FGF-21 Agreement), which was followed by a formal notification on July 18, 2022 to be effective three months from receipt of the formal notification date. Due to this termination notice and the Company's determination that the asset had no alternative future use, the Company concluded the net carrying value of the BMS FGF-21 intangible asset was greater than its estimated fair value and therefore recorded an impairment charge of \$7.2 million.

The Company's intangible assets also include acquired in-process research and development (IPR&D) from a business combination, which is recognized as an indefinite lived intangible asset until completion or abandonment of the related R&D activities. When the related R&D activity is completed, the IPR&D intangible asset is reclassified as a finite-lived intangible asset and amortized over the remaining useful life. The Company's acquired IPR&D is tested for impairment annually or more frequently if events or changes in circumstances between annual tests indicate that the asset may be impaired. On October 18, 2022, the Company announced a reprioritization of its product pipeline after conducting a strategic assessment that considered its cash runway and its product pipeline near term value creation opportunities, among other factors. As a result of this assessment, the Company paused its internal development of ARX788 and, among other potential activities, indicated it will seek development partners to further the development of ARX788 outside of China. The Company determined this reprioritization was a qualitative trigger of potential impairment of its IPR&D asset and had a quantitative analysis completed as of the reprioritization date. The quantitative analysis determined the IPR&D asset was not impaired as of the reprioritization date.

The Company's annual impairment test for the years ended December 31, 2022 and 2021, performed in the fourth quarter, did not result in additional impairment losses related to its intangible assets.

While the Company's current and historical operating losses and negative cash flows are possible indicators of impairment, management believes future cash flows to be generated by its remaining long-lived assets support the carrying value.

Fair Value of Financial Instruments

The Company's financial instruments consist primarily of cash and cash equivalents, MDS, accounts receivable, accounts payable and accrued liabilities. The carrying amounts of cash and cash equivalents, accounts receivable, accounts payable and accrued liabilities are considered to be representative of their respective fair values because of the relatively short-term nature of those instruments.

The accounting guidance defines fair value, establishes a consistent framework for measuring fair value and expands disclosure for each major asset and liability category measured at fair value on either a recurring or nonrecurring basis. Fair value is defined as an exit price, representing the amount that would be received to sell an asset or paid to transfer a liability in an orderly transaction between market participants. As such, fair value is a market-based measurement that should be determined based on assumptions that market participants would use in pricing an asset or liability. As a basis for considering such assumptions, the accounting guidance establishes a three-tier fair value hierarchy, which prioritizes the inputs used in measuring fair value as follows:

Level 1: Inputs based on quoted market prices for identical assets or liabilities in active markets at the measurement date.

Level 2: Observable inputs other than quoted prices included in Level 1, such as quoted prices for similar assets and liabilities in active markets; quoted prices for identical or similar assets and liabilities in markets that are not active; or other inputs that are observable or can be corroborated by observable market data.

Level 3: Inputs which reflect management's best estimate of what market participants would use in pricing the asset or liability at the measurement date. The inputs are unobservable in the market and significant to the instrument's valuation.

Assets and liabilities are classified based on the lowest level of input that is significant to the fair value measurements. The Company reviews the fair value hierarchy classification on a quarterly basis.

Clinical Trial Accruals

As part of the process of preparing the consolidated financial statements, the Company is required to estimate expenses resulting from obligations under contracts with vendors, clinical research organizations, consultants and under clinical site agreements relating to conducting clinical trials. The financial terms of these contracts vary and may result in payment flows that do not match the periods over which materials or services are provided under such contracts.

The Company's objective is to reflect the appropriate clinical trial expenses in its consolidated financial statements by recording those expenses in the period in which services are performed and efforts are expended. The Company accounts for these expenses according to the progress of the clinical trial as measured by patient progression and the timing of various aspects of the clinical trial. Management determines accrual estimates, as of each balance sheet date, through discussions with applicable personnel and outside service providers as to the progress of clinical trials. During a clinical trial, the Company adjusts its expense recognition if actual results differ from previous estimates.

Leases

The Company determines if an arrangement is a lease at the inception of the contract. The asset component of the Company's operating leases is recorded as a ROU asset and the liability component is recorded as current portion of operating lease liabilities and operating lease liabilities, net of current portion, in the consolidated balance sheets.

At the commencement, reassessment or modification date, the cost of the ROU asset includes all the following, if any: the amount of the initial measurement of the lease liability, any lease payments made to the lessor at or before the commencement date minus any lease incentive received and any initial direct costs incurred by the lessee. Operating lease liabilities are recognized based on the present value of lease payments over the lease term at the commencement date. The Company uses an incremental borrowing rate based on the information available at commencement date in determining the present value of lease payments if an implicit rate of return is not provided within the lease contract. When evaluating its incremental borrowing rate, management considers its borrowing rate on external collateralized debt with a term commensurate with the lease term, if any, or in the absence of external debt, the average incremental borrowing rate of its peer group. These amounts are estimated at the inception of or upon reassessment of a lease arrangement.

Lease cost is recognized on a straight-line basis over the lease term, and includes amounts related to short-term leases. Variable lease costs, such as common area maintenance, real estate taxes and management fees which do not depend on an index or rate are recognized as incurred. Short-term leases of 12 months or less are expensed as incurred, which approximates the straight-line basis due to the short-term nature of the leases. The Company has elected not to separate lease and non-lease components.

ROU assets and operating lease liabilities are remeasured upon lease reassessment using the present value of remaining lease payments and estimated incremental borrowing rates. The Company reviews any changes to its lease agreements for potential modifications and/or indicators of impairment of the respective ROU asset.

Revenue Recognition

The Company determines revenue recognition for arrangements within the scope of ASC Topic 606, *Revenue from Contracts with Customers* (ASC 606) by performing the following five steps: (i) identify the contract; (ii) identify the performance obligations in the contract; (iii) determine the transaction price; (iv) allocate the transaction price to the performance obligations in the contract; and (v) recognize revenue when, or as, the Company satisfies a performance obligation. A performance obligation is a promise in a contract to transfer a distinct good or service and is the unit of accounting in ASC 606. A contract's transaction price is allocated among each distinct performance obligation based on relative standalone selling price and recognized as revenue when, or as, the applicable performance obligation is satisfied.

The terms of the Company's R&D Agreements include upfront fees, R&D funding or reimbursements, milestone and other contingent payments for the achievement of defined objectives and certain preclinical, clinical, regulatory and sales-based events, as well as royalties on sales of commercialized products. Agreements with certain upfront payments may require deferral of revenue recognition to a future period until the Company performs the obligations under these agreements. The Company uses the most likely amount method to estimate variable consideration for event-based milestones and other contingent payments and have been fully constrained given the degree of uncertainty around the occurrence of such events. The Company continues to re-evaluate the transaction price in each reporting period as contingencies are resolved and other changes in circumstances occur.

The Company is required to adjust the transaction price for the effects of the time value of money if the timing of payments agreed to by the parties to the contract, explicitly or implicitly, provides the Company or its customer with a significant benefit of financing the transfer of goods or services. The Company concluded that its contracts with the customers do not contain a significant financing component because the payment structure of the R&D Agreements arises from reasons other than providing a significant benefit of financing.

Taxes assessed by a governmental authority that are both imposed on and concurrent with a specific revenue-producing transaction, that are collected by the Company from a customer, are excluded from revenues.

R&D Agreements

The Company analyzes its R&D Agreements to assess whether they are within the scope of ASC Topic 808, *Collaborative Arrangements* (ASC 808), which includes determining whether such arrangements involve joint operating activities performed by parties that are both active participants in the activities and exposed to significant risks and rewards dependent on the commercial success of such activities. This assessment is performed at contract inception and again, if changes in either the roles of the participants in the arrangement or the participants' exposure to significant risks and rewards dependent on the ultimate commercial success of the arrangement are identified. For each of the periods presented, the Company determined that its contracts with customers do not fall within the guidance in ASC 808 as the Company is not exposed to significant risks that are dependent on commercial success of the collaborative activity.

License Fees

As part of the R&D Agreements, the Company licenses its intellectual property to customers for fees, which many times includes the receipt of upfront fees. If a license to the Company's intellectual property is determined to be distinct from the other promises or performance obligations identified in the agreement, the Company recognizes revenue from non-refundable, upfront fees allocated to the license when the license is transferred to the customer.

In assessing whether a promise or performance obligation is distinct from the other promises, the Company considers factors such as the research, development, manufacturing and commercialization capabilities of the licensee and the availability of the associated expertise in the general marketplace. In addition, the Company considers whether the licensee can benefit from a promise for its intended purpose without the receipt of the remaining promise, whether the value of the promise is dependent on the unsatisfied promise, whether there are other vendors that could provide the remaining promise, and whether it is separately identifiable from the remaining promise. For licenses that are combined with other promises, the Company utilizes judgment to assess the nature of the combined performance obligation to determine whether the combined performance obligation is satisfied over time or at a point in time and, if over time, the appropriate method of measuring progress for purposes of recognizing revenue. For those license related performance obligations that are satisfied over time, the Company measures progress through actual effort, including hours incurred, and an estimation of time to completion based on the budget and research workplan.

Typical agreements require the transfer of knowledge so the customer can effectively use the license and the Company believes these measurements accurately represent the transfer of knowledge through its clinical research services. The Company evaluates the measure of progress each reporting period and, if circumstances change over time, the Company will update its measure of progress to reflect any changes in the outcome of the performance obligation and, therefore, adjust the measure of performance and related revenue recognition. The measure of progress, and thereby periods over which revenue should be recognized, is subject to estimates by management and may change over the course of the agreement. Such a change could have a material impact on the amount of revenues the Company records in future periods.

During the second half of 2021, the Company re-evaluated the measure of progress for a compound under one of its R&D Agreements, which resulted in an increased estimate in the timing and efforts of satisfaction of the Company's performance obligations under the agreement. This change did not have an impact on the transaction price and/or the variable consideration to be received under the agreement. As a result of the re-evaluation, the Company recognized a cumulative catch-up adjustment reducing revenue by approximately \$1.4 million with an equal increase in total contract liabilities (i.e., deferred revenue) from upfront payments as of December 31, 2021. The Company's periodic reassessments, during the year ended December 31, 2022, did not result in any adjustments to its current revenue recognition methodology.

Reimbursements

As part of the R&D Agreements where the Company only provides R&D services, the Company is reimbursed by the customer for certain costs incurred as agreed to in the research plan. The Company elected the practical expedient for certain R&D reimbursements which allows it to recognize revenue in the amount for which the Company has a right to invoice if its right to consideration is an amount corresponding directly to the value of completed performance to date. The Company estimates variable consideration, if any, at contract inception and each reporting period, to determine if there were any changes in the transaction price. The transaction price will be adjusted to the extent the risk of significant revenue reversal in the amount of cumulative revenue recognized will not occur when the uncertainty associated with the milestones are subsequently resolved. Any such adjustments are recorded on a cumulative catch-up basis and revenues and earnings are impacted in the period of adjustment.

Milestones and Other Contingent Payments

At the inception of each R&D Agreement that includes milestones and other contingent payments, the Company evaluates whether the milestones or other contingent payments are considered probable of being achieved and estimates the amount to be included in the initial transaction price using the most likely amount method. If it is probable that a significant revenue reversal would not occur, the associated value is included in the transaction price. Milestones or other contingent payments are only included in the transaction price to the extent the risk of a significant revenue reversal in the amount of cumulative revenue recognized will not occur when the uncertainty associated with the milestones are subsequently resolved. The Company evaluates factors such as the scientific, clinical, regulatory, commercial, and other risks that must be overcome to achieve the particular contingency in making this assessment. There is considerable judgment involved in determining whether it is probable that a significant revenue reversal would not occur. At the end of each subsequent reporting period, the Company reevaluates the probability of achievement of all milestones and other contingencies subject to constraint and, if necessary, adjusts its estimate of the overall transaction price. Any such adjustments are recorded on a cumulative catch-up basis and revenues and earnings are impacted in the period of adjustment.

Sales-Based Milestones and Royalties on Sales of Commercialized Products

For R&D Agreements that include sales-based milestone payments and royalties which are the result of a customer-vendor relationship and for which the license is deemed to be the predominant item to which the royalties relate, the Company recognizes revenue at the later of (i) when the related sales occur, or (ii) when the performance obligation to which some or all of the royalty has been allocated has been satisfied or partially satisfied.

R&D Services

Promises under the Company's R&D Agreements may include R&D services to be performed by the Company on behalf of the counterparty. If these services are determined to be distinct from the other promises or performance obligations identified in the arrangement, the Company recognizes the transaction price allocated to these services as revenue over time based on an appropriate measure of progress of the performance. If these services are determined not to be distinct from the other promises or performance obligations identified in the arrangement, the Company recognizes the transaction price allocated to the combined performance obligation as the related performance obligation is satisfied. For those R&D services that are satisfied over time, the Company, measures progress through actual effort, including hours incurred, and an estimation of time to completion based on the budget and research workplan. Typical agreements require the transfer of knowledge and development of drug products and the Company believes these measurements accurately represent the transfer of clinical research services.

Customer Options

If an arrangement contains customer options, the Company evaluates whether the options are material rights because they allow the customer to acquire additional goods or services for free or at a discount incremental to the range of discounts typically given to a similar class of customers. If the customer options are determined to represent a material right, the material right is recognized as a separate performance obligation at the outset of the arrangement. The Company allocates the transaction price to material rights based on the relative stand-alone selling price, which is determined based on the identified discount and the probability that the customer will exercise the option. Amounts allocated to a material right are not recognized as revenue until, at the earliest, the future goods or services are transferred or upon expiration of the option. If the options are deemed not to be a material right, they are excluded as performance obligations at the outset of the arrangement.

Research and Development Expense

R&D expenses consist primarily of costs incurred in connection with the development of the Company's technology platform, product candidates, discovery efforts and preclinical and clinical development of its product candidates. The Company's research and development expenses include third-party costs with contract research organizations, contract manufacturing organizations and others conducting R&D activities and clinical trials on the Company's behalf, manufacturing costs, outside consultant costs, laboratory supply and clinical trial material costs, and license payments for intellectual property used in R&D activities. The Company's R&D expenses also include personnel costs, such as salaries, benefits, and other employee related costs, including share-based compensation, for personnel engaged in the Company's R&D functions, amortization of finite-lived intangible assets, facility and equipment related costs, which include depreciation and amortization costs and expenses for rent and maintenance of facilities and other operating costs if specifically identifiable to R&D activities.

General and Administrative Expense

General and administrative (G&A) expenses include personnel costs, such as salaries and other related costs, including share-based compensation, for personnel in the Company's executive, finance, business development, information technology, human resources, operations and administrative functions. G&A expenses also include legal fees relating to intellectual property and corporate matters, professional fees for accounting, auditing, tax and consulting services, insurance costs, travel expenses, facilities-related costs, which include depreciation costs and expenses for rent and maintenance of facilities, and other operating costs that are not specifically attributable to research activities.

Patent Expenses

The Company expenses all patent costs as incurred in connection with patent applications, including direct application fees, and the legal and consulting expenses related to making such applications, and such costs are included in G&A expenses in the consolidated statements of operations and comprehensive loss.

Share-Based Compensation

The Company accounts for share-based compensation under the provisions of ASC Topic 718, *Compensation—Stock Compensation*. The Company estimates the fair value of each option award on the date of grant using the Black-Scholes option pricing model (BSM). The BSM requires the use of highly subjective assumptions, including, but not limited to, expected share price volatility over the term of the awards and the expected term of the options.

The Company recognizes share-based compensation expense on a straight-line basis based upon the grant date fair value. For awards whose vesting is based upon satisfaction of both a requisite service period and a performance criterion, the Company records share-based compensation expense on a straight-line basis until the earlier of the completion of the explicit service period or the achievement of the performance criteria. Performance criteria for awards subject to regulatory approval do not become probable of occurrence until the board of director's reviews and approves the satisfaction of the performance criteria. The Company recognizes the effect of forfeitures in compensation cost in the period that the award was forfeited. See *Note 11—Share-Based Compensation* for information on the assumptions used in determining the grant date fair value.

Income Taxes

The Company uses the asset and liability method of accounting for income taxes. Under this method, deferred tax assets and liabilities are determined based on the difference between the financial reporting and the tax reporting basis of assets and liabilities and are measured using the enacted tax rates and laws that are expected to be in effect when the differences are expected to reverse. The Company provides a valuation allowance against net deferred tax assets unless, based upon the available evidence, it is more likely than not that the deferred tax assets will be realized. When the Company establishes or reduces the valuation allowance against its deferred tax assets, its provision for income taxes will increase or decrease, respectively, in the period such determination is made.

The accounting guidance for uncertainty in income taxes prescribes a recognition threshold and measurement attribute criteria for the financial statement recognition and measurement of tax positions taken or expected to be taken in a tax return. For those benefits to be recognized, a tax position must be more likely than not to be sustained upon examination by taxing authorities based on the technical merits of the position. Interest and penalties, if any, related to unrecognized income tax positions are recognized in provision for income taxes, in the consolidated statements of operations and comprehensive loss.

Net Loss Per Share Attributable to Ambrx Biopharma Inc Ordinary Shareholders

Basic net loss per ordinary share is calculated by dividing the net loss attributable to ordinary Ambrx shareholders by the weighted-average number of ordinary shares outstanding during the period, without consideration for potentially dilutive securities. Diluted net loss per share is computed by dividing the net loss attributable to ordinary shareholders by the weighted-average number of ordinary shares and potentially dilutive securities outstanding for the period determined using the treasury-stock and if-converted methods. For purposes of the diluted net loss per share calculation, potentially dilutive securities are excluded from the calculation of diluted net loss per share because their effect was anti-dilutive and therefore, basic and diluted net loss per share were the same for all periods presented.

Potentially dilutive securities excluded from the calculation of diluted net loss per share included options to purchase 39,116,174 and 34,200,976 ordinary shares for the years ended December 31, 2022 and 2021, respectively.

Foreign Currency

The functional currency of Ambrx HK, Ambrx US and Ambrx AU is the U.S. dollar. Through June 30, 2021, the functional currency for Ambrx Shanghai was the Chinese Renminbi. The financial statements of Ambrx Shanghai were translated into U.S. dollars using exchange rates in effect at each period-end for assets and liabilities and average exchange rates during the period for results of operations. Upon completion of the Reorganization, Ambrx Shanghai became the Company's wholly owned subsidiary at which time their functional currency became the U.S. dollar.

The adjustment resulting from translating the financial statements of the Company's then majority-owned subsidiary was reflected in accumulated other comprehensive loss in the Company's consolidated balance sheets. Foreign currency transaction gains and losses are reported as other income (expense), net, in the consolidated statements of operations and comprehensive loss. Foreign currency transaction gains and losses during the years ended December 31, 2022 and 2021, were not material.

Noncontrolling Interests

Through March 31, 2021, revenues, expenses, gains, losses, net loss and other comprehensive loss were reported in the consolidated financial statements at the consolidated amounts, which included the amounts attributable to both the controlling and redeemable noncontrolling interests.

Prior to March 2021, the Company's noncontrolling interest was redeemable and classified outside of permanent equity because upon certain contingent events not being solely within the Company's control it may be required to purchase the Company's RNCI. In March 2021, upon execution of the Reorganization agreements, the Company's noncontrolling interests became mandatorily redeemable with embedded derivatives and were therefore reclassified from outside of permanent equity to a current liability until settlement at which time the RNCI was no longer subject to allocation of losses or other comprehensive loss.

Reclassification

To conform with current year presentation of the Company's impairment of intangible assets, prior period amounts have been reclassified in the consolidated statements of operations and comprehensive loss.

Recent Accounting Pronouncements

From time to time, new accounting pronouncements are issued by the Financial Accounting Standards Board or other standards setting bodies that are adopted as of the specified effective date. The Company believes the impact of recently issued standards and any issued but not yet effective standards will not have a material impact on its consolidated financial statements upon adoption.

3. Balance Sheet Details

Prepaid Expenses and Other Current Assets

Prepaid expenses and other current assets consist of the following as of December 31, (in thousands):

	2022	2021
Tax receivable	\$ 1,506	\$ 104
Prepaid R&D costs	1,476	2,467
Prepaid insurance and service contracts	1,424	1,860
Interest receivable - marketable debt securities	168	—
Other	319	230
Total	<u>\$ 4,893</u>	<u>\$ 4,661</u>

Property and Equipment, Net

Property and equipment, net, consist of the following as of December 31, (in thousands):

	2022	2021
Laboratory equipment	\$ 7,559	\$ 6,851
Computers, software and office equipment	512	489
Leasehold improvements	467	384
Office furniture and fixtures	123	126
	8,661	7,850
Accumulated depreciation and amortization	(5,617)	(4,866)
Total	<u>\$ 3,044</u>	<u>\$ 2,984</u>

Depreciation and amortization expense for property and equipment for the years ended December 31, 2022 and 2021 was \$0.8 million and \$0.6 million, respectively.

Accrued Liabilities

Accrued liabilities consist of the following as of December 31, (in thousands):

	2022	2021
Accrued R&D costs ⁽¹⁾	\$ 4,069	\$ 9,043
Accrued compensation	3,494	3,664
Accrued audit, tax and filing fees	1,703	556
Accrued directors and officers insurance premium financing obligation ⁽²⁾	926	—
Accrued other	1,122	862
Total	<u>\$ 11,314</u>	<u>\$ 14,125</u>

(1) Includes \$99 and \$250 of accrued R&D costs due to related parties as of December 31, 2022 and 2021, respectively.

(2) Represents the remaining balance due under the Company's insurance premium financing agreement, which is payable in equal monthly installments through May 2023 and bears interest at approximately 3.4% per annum.

4. Intangible Assets, Net

Intangible assets, net, consist of the following as of and for the year ended December 31, 2022 (in thousands, except years):

	Weighted-Average Remaining Contractual Life (in years)	Gross Carrying Amount	Impairment ⁽¹⁾	Accumulated Amortization	Intangible Assets, Net
Acquired technologies	8.8	\$ 24,330	\$ (9,660)	\$ (10,360)	\$ 4,310
IPR&D		20,940	—	—	20,940
Total		<u>\$ 45,270</u>	<u>\$ (9,660)</u>	<u>\$ (10,360)</u>	<u>\$ 25,250</u>

(1) Includes the impairment of BMS Relaxin and BMS FGF-21 intangible assets, as more fully described within the Intangible Assets, Net subsection of Note 2—Summary of Significant Accounting Policies. These intangible asset impairments are presented in the consolidated statements of operations and comprehensive loss as impairment of intangible assets within operating activities.

Intangible assets, net, consist of the following as of and for the year ended December 31, 2021 (in thousands, except years):

	Weighted-Average Remaining Contractual Life (in years)	Gross Carrying Amount	Additions	Impairment ⁽¹⁾	Accumulated Amortization	Intangible Assets, Net
Acquired technologies	9.7	\$ 23,870	\$ 1,250	\$ (513)	\$ (9,585)	\$ 15,022
IPR&D		20,940	—	—	—	20,940
Total		<u>\$ 44,810</u>	<u>\$ 1,250</u>	<u>\$ (513)</u>	<u>\$ (9,585)</u>	<u>\$ 35,962</u>

(1) Represents the impairment of an acquired technology intangible asset, as more fully described within the Intangible Assets, Net subsection of Note 2—Summary of Significant Accounting Policies. These intangible asset impairments are presented in the consolidated statements of operations and comprehensive loss as impairment of intangible assets within operating activities.

Amortization expense for intangible assets for the years ended December 31, 2022 and 2021 was \$1.1 million and \$1.6 million, respectively.

Future amortization expense is as follows as of December 31, 2022 (in thousands):

<u>Year ending December 31,</u>	
2023	\$ 629
2024	630
2025	629
2026	364
2027	356
Thereafter	1,702
Total	<u>\$ 4,310</u>

5. Marketable Debt Securities, Available-for-Sale

The following table summarizes the Company's MDS as of December 31, 2022 (in thousands):

	Weighted-Average Remaining Contractual Life (in years)	Amortized Costs	Unrealized Gains	Unrealized Losses	Fair Value
Classified as current assets:					
Commercial paper	1 or less	\$ 15,803	\$ 1	\$ (23)	\$ 15,781
Certificates of deposit	1 or less	7,500	2	(25)	7,477
U.S. government securities	1 or less	5,001	—	(30)	4,971
Corporate bonds	1 or less	646	—	(2)	644
Total Marketable debt securities, available-for-sale	1 or less	\$ 28,950	\$ 3	\$ (80)	\$ 28,873
Classified as non-current assets:					
U.S. government securities	1.4	\$ 6,979	\$ —	\$ (184)	\$ 6,795
Corporate bonds	1.5	6,824	—	(192)	6,632
Asset backed securities	1.8	2,999	—	(45)	2,954
Non-U.S. government securities	1.5	423	—	(11)	412
Total Marketable debt securities, available-for-sale, net of current portion	1.5	\$ 17,225	\$ —	\$ (432)	\$ 16,793
Total	0.7	\$ 46,175	\$ 3	\$ (512)	\$ 45,666

As of December 31, 2022, interest receivables related to MDS of \$0.2 million are included in prepaid expenses and other current assets in the consolidated balance sheets.

Accumulated unrealized losses on MDS that have been in a continuous loss position for less than 12 months and for more than 12 months as of December 31, 2022, were as follows (in thousands):

	Less than 12 months		More than 12 months	
	Estimated Fair Value	Gross Unrealized Losses	Estimated Fair Value	Gross Unrealized Losses
Commercial paper	\$ 12,803	\$ (22)	\$ —	\$ —
U.S. government securities	11,765	(216)	—	—
Corporate bonds	7,276	(193)	—	—
Certificates of deposit	2,975	(25)	—	—
Asset backed securities	2,954	(45)	—	—
Non-U.S. government securities	412	(11)	—	—
Total	\$ 38,185	\$ (512)	\$ —	\$ —

As of December 31, 2022, a total of 22 of the securities were in an unrealized loss position. The Company evaluated its MDS and concluded that the losses were caused by interest rate fluctuations, as opposed to credit quality. Because the Company does not intend to sell its MDS and it is not more likely than not that the Company will be required to sell its MDS before recovery of their amortized cost bases, which may be maturity, the Company does not consider its MDS to be impaired.

Realized gains and losses on MDS were not significant for the year ended December 31, 2022.

6. Fair Value Measurements

The following table presents the Company's financial assets measured at fair value on a recurring basis as of December 31, 2022 (in thousands):

	Total	Level 1	Level 2	Level 3
Cash equivalents:				
Certificates of deposit	\$ 24,000	\$ —	\$ 24,000	\$ —
Commercial paper	15,352	—	15,352	—
Money market funds	12,743	12,743	—	—
Total cash equivalents	<u>\$ 52,095</u>	<u>\$ 12,743</u>	<u>\$ 39,352</u>	<u>\$ —</u>
Marketable debt securities, available-for-sale:				
Commercial paper	\$ 15,781	\$ —	\$ 15,781	\$ —
Certificates of deposit	7,477	—	7,477	—
U.S. government securities	4,971	—	4,971	—
Corporate bonds	644	—	644	—
Total Marketable debt securities, available-for-sale	<u>\$ 28,873</u>	<u>\$ —</u>	<u>\$ 28,873</u>	<u>\$ —</u>
Marketable debt securities, available-for-sale, net of current portion:				
U.S. government securities	\$ 6,795	\$ —	\$ 6,795	\$ —
Corporate bonds	6,632	—	6,632	—
Asset backed securities	2,954	—	2,954	—
Non-U.S. government securities	412	—	412	—
Total Marketable debt securities, available-for-sale, net of current portion	<u>\$ 16,793</u>	<u>\$ —</u>	<u>\$ 16,793</u>	<u>\$ —</u>

As of December 31, 2021, the Company had \$162.6 million, in cash equivalents which consisted of money market funds which were valued based on quoted market prices for identical assets in active markets at their measurement date.

During the years ended December 31, 2022 and 2021, there were no transfers into or out of Level 3 of the fair value hierarchy.

As of December 31, 2022 and 2021, the Company had no liabilities measured at fair value on a recurring basis.

7. Commitments and Contingencies

Intellectual Property Licenses

Lonza

On December 11, 2019, the Company entered into a commercial license agreement with Lonza Sales AG (Lonza) for a fully paid-up license to use Lonza's GS System with the Company's non-natural amino acid technology (the 2019 Agreement). This agreement replaces the prior agreements the Company entered into with Lonza for the GS system in 2009 and 2015. The 2019 Agreement, as amended, includes an option to evaluate and sublicense Lonza's piggyBac Expression Technology Patent Rights with the Company's technology. Under the 2019 Agreement, the Company paid a license fee of approximately 2.0 million Swiss Francs (or approximately \$2.1 million) for the fully paid up license to the GS System and had an option to a license to Lonza's piggyBac technology with the Company's non-natural amino acid technology. The Company notified Lonza effective July 1, 2022, that it will not exercise the option and will no longer pursue further development efforts related to the piggyBac technology.

The Scripps Research Institute

In August 2003, the Company entered into a license agreement with The Scripps Research Institute (TSRI) for the development and commercialization and right to sublicense products using TSRI materials and technology (the TSRI Agreement). Under the TSRI Agreement, the Company is obligated to pay royalties in the low single-digits based on the amount of annual sales for licensed products and sublicensing royalties of licensed products in the low single-digits on annual sublicensing revenues, if any. During the years ended December 31, 2022 and 2021, the Company's payments to TSRI were \$0.1 million and \$1.7 million, respectively.

Litigation

From time to time, the Company may be involved in various lawsuits, legal proceedings, or claims that arise in the ordinary course of business. Management believes there are no claims or actions pending against the Company as of December 31, 2022 which will have, individually or in the aggregate, a material adverse effect on its business, liquidity, financial position, or results of operations. Litigation, however, is subject to inherent uncertainties, and an adverse result in these or other matters may arise from time to time that may harm the Company's business.

Indemnification

In accordance with the Company's amended and restated memorandum and articles of association, the Company has indemnification obligations to its officers and directors for certain events or occurrences, subject to certain limits, while they are serving in such capacity. There have been no claims to date, and the Company has a directors and officers liability insurance policy that may enable it to recover a portion of any amounts paid for future claims.

8. Leases

The Company has operating leases for its corporate offices and certain equipment. The leases have remaining lease terms of approximately two to five years. The Company is responsible for payment of taxes and operating expenses for the building, in addition to monthly base rent in the initial amount of approximately \$0.1 million, with 3% annual increases. Upon execution of the lease in March 2005, the Company provided a security deposit of approximately \$0.3 million which is included in other long-term assets in the consolidated balance sheets. The Company has determined that the lease is an operating lease for accounting purposes.

In March 2005, the Company executed a lease for approximately 36,000 square feet. Effective December 1, 2021, the Company exercised its option to extend its existing facility lease for an additional five years (the Lease Amendment) through November 30, 2027. Upon delivery of the Company's notice to exercise the right to extend the term option in the lease, the Company reassessed its facility lease. In December 2021, upon determination of the lease payments, the Company again reassessed its facility lease. The reassessments of the Lease Amendment was determined to qualify as a change of accounting for the existing lease rather than a separate contract. As such, the ROU assets and operating lease liabilities were remeasured using an incremental borrowing rate as of the reassessment date. The Company determined there was no difference between the remeasured ROU asset and the operating lease liabilities and therefore no gain or loss was recognized and no impairment of the ROU asset occurred. During the fourth quarter of 2021, the Company recorded an increase in the ROU assets and lease liabilities of \$11.5 million. The Company no longer has a right to extend the lease term.

The components of lease expense are as follows for the years ended December 31, (in thousands):

	2022	2021
Operating lease expenses R&D:		
Operating lease costs	\$ 2,217	\$ 1,203
Variable lease costs ⁽¹⁾	1,090	1,190
Operating lease expenses G&A:		
Operating lease costs	509	232
Variable lease costs ⁽¹⁾	236	231
Total operating leases expense	\$ 4,052	\$ 2,856

(1) Includes short-term lease costs which are immaterial.

Supplemental balance sheet information related to operating leases is as follows as of December 31, (in thousands):

	2022	2021
ROU assets, net	\$ 10,968	\$ 12,737
Operating lease liabilities, current	\$ 1,734	\$ 915
Operating lease liabilities, net of current	\$ 10,245	\$ 12,212

Supplemental cash flow information related to leases is as follows for the years ended December 31, (in thousands):

	2022	2021
Cash paid for amounts included in the measurement of lease liabilities:		
Operating cash flows used for operating leases	\$ 1,874	\$ 1,742
Weighted-average remaining lease term in years	4.9	5.9
Weighted-average discount rate	7.63%	7.63%

Future lease liabilities are as follows as of December 31, 2022 (in thousands):

<u>Year ending December 31,</u>	
2023	\$ 2,814
2024	2,896
2025	2,982
2026	3,071
2027	2,892
Thereafter	—
	14,655
Less interest expense	(2,676)
Total	\$ 11,979

9. Ordinary Shares and Convertible Preferred Shares

Ordinary Shares

As described in *Note 1—Description of Business and Basis of Presentation*, the Company completed an IPO in June 2021 of 7,000,000 ADSs (i.e., 49,000,000 ordinary shares) and the issuance of 892,831 ADSs (i.e., 6,249,817 ordinary shares). Each ADS represents seven ordinary shares of the Company.

At-the-Market Offering Agreement

On July 29, 2022, the Company entered into an at-the-market sales agreement with Cowen and Company LLC, pursuant to which the Company was able to offer and sell its ADSs, each representing seven of the Company's ordinary shares, having an aggregate offering price of up to \$80.0 million (the ATM Program). During the first quarter of 2023, the Company issued and sold 16,575,826 of its ADSs at an average selling price of \$4.83 per ADS, for gross proceeds of approximately \$80.0 million, less sales commissions of approximately \$2.0 million, for net proceeds of approximately \$78.0 million. Accordingly, as of March 10, 2023, the ATM Program is complete.

Convertible Preferred Shares

During the year ended December 31, 2021, the Company's Series A and Series B convertible preferred shares were classified as temporary equity instead of shareholders' equity in accordance with U.S. GAAP for the classification and measurement of potentially redeemable securities, as the shares were conditionally redeemable upon certain change in control events that are outside the Company's control, including the liquidation, sale, or transfer of control of the Company. Upon such change in control events, holders of the convertible preferred shares could cause its redemption. Upon completion of the Company's IPO, the Series A and Series B convertible preferred shares were automatically converted into ordinary shares and are no longer outstanding.

Amended and Restated Memorandum of Association

Concurrent with the closing of the IPO, the Company amended and restated its memorandum of association which authorizes the issuance of 500,000,000 ordinary shares and 100,000,000 of such class or classes (however designated) of shares as the Company's board of directors may determine (the Undesignated Shares). As of December 31, 2022, the Company has no issued or outstanding Undesignated Shares.

In February 2023, the Company's board of directors designated the previously Undesignated Shares as ordinary shares. Accordingly, following this designation the Company had 600,000,000 authorized ordinary shares.

10. Revenues

During the years ended December 31, 2022 and 2021, the Company recognized revenue over time under each of its R&D Agreements as its performance obligations were satisfied. Variable consideration, such as development and regulatory milestones previously constrained is recognized to the extent a significant revenue reversal in the amount of cumulative revenue recognized will not occur when the uncertainty associated with the variable consideration is subsequently resolved.

Revenue recognized was earned under the Company's R&D Agreements and is summarized below based on the nature of payment type for the years ended December 31, (in thousands):

<u>Timing of Transfer of Goods or Services</u>	<u>2022</u>	<u>2021</u>
Over time:		
License fees ⁽¹⁾	\$ 3,442	\$ 3,533
R&D services	2,140	2,072
Reimbursements	820	1,850
Point in time:		
Milestones	1,000	—
Total revenues	<u>\$ 7,402</u>	<u>\$ 7,455</u>

- (1) 2021 license fees include a cumulative catch-up adjustment reducing revenue by approximately \$1.4 million with an equal increase in total contract liabilities as of December 31, 2021, for changes in total estimated effort to be incurred in the future to satisfy the performance obligation.

Remaining Performance Obligations and Deferred Revenue

As of December 31, 2022 and 2021, unsatisfied remaining performance obligations for minimum full-time equivalent (FTE) services under the Company's R&D Agreements totaled \$0.1 million and \$1.2 million, respectively. As of December 31, 2022, the Company expects to recognize the remaining deferred revenue related to R&D services under its existing R&D Agreements during the year ended December 31, 2023.

In addition, as of December 31, 2022 and 2021, the Company had deferred revenue of \$1.7 million and \$5.7 million, respectively, which was primarily related to (i) the combined performance obligation for transfer of the Company's license and R&D services and (ii) conducting R&D activities, which are a separate performance obligation in the Company's contracts pursuant to research plans under the R&D agreements. The Company anticipates that the remaining performance obligations as of December 31, 2022 will be satisfied over the next one to four years.

Zhejiang Medicine Co. Ltd. (ZMC)

In June 2013, the Company entered into a co-development and license agreement with ZMC to develop and commercialize ARX788 (the ZMC Agreement). In March 2019, the ZMC Agreement was transferred to NovoCodex Biopharmaceutical Ltd (NovoCodex), a subsidiary of ZMC. Under the ZMC Agreement, both companies will continue the development of ARX788. ZMC is responsible, at its sole expense, for making commercially reasonable efforts to develop, obtain regulatory approval for and commercialize the licensed products in China and fund the development of the product in Australia or other jurisdictions approved by a joint steering committee through Phase 1 clinical trials. ZMC will receive commercial rights in China while Ambrx retains commercial rights outside of China and will receive low double-digit tiered royalties on sales of the product in China.

Under the terms of the ZMC Agreement, as amended, ZMC received an exclusive right and license for the prevention, and treatment of human diseases and conditions associated with α Her2 with the right to grant sublicenses under the Company's existing patents and know how. Under the agreement, the Company is entitled to receive tiered royalties as high as mid-teens range on aggregate net sales of ARX788 in the People's Republic of China (PRC). The Company will be entitled to receive these royalties until the later of the expiration of the applicable patent rights or 20 years after the first commercial sale of the product in the PRC. In addition, the Company is obligated to pay royalties in a mid-single digit to low-teens percentage range of any sublicensing profit that the Company may receive outside of the PRC, depending on what phase of clinical development has been completed at the time of transfer, or a low single digit percentage range on any net sales that the Company or its successors may receive from sales of ARX788 outside of the PRC, if the market authorization of ARX788 is based on Phase 1 clinical data obtained during the Company's collaboration with ZMC.

BeiGene Ltd. (BeiGene)

In March 2019, the Company entered into a collaboration and exclusive license agreement with BeiGene for the development and commercialization of next-generation biologics drugs (the BeiGene Agreement) and received an upfront license payment to fund the initial discovery and research activities of \$10.0 million. Under the terms of the BeiGene Agreement, BeiGene will have worldwide rights to develop and commercialize any drug products resulting from the collaboration. BeiGene may terminate the BeiGene Agreement upon three months' written notice. The Company or BeiGene may terminate the BeiGene Agreement for cause for safety reasons or upon other party's material breach that remains uncured after receipt of notice thereof, or upon certain bankruptcy or insolvency proceedings. The Company may also terminate the BeiGene Agreement for cause due to BeiGene's failure to use commercially reasonable efforts in the development and commercialization of products.

The Company is eligible to receive payments for R&D services performed by its employees based on the annual rate per FTE defined in the agreement, for a minimum of two and up to 25 FTEs. BeiGene will reimburse third-party costs incurred by the Company as agreed to per the BeiGene Agreement. The Company is also eligible to receive additional upfront payments if BeiGene elects to initiate additional programs and milestone payments upon achievement of certain potential development, regulatory, and sales-based milestones for all programs. The Company is also entitled to receive tiered royalties on a product-by-product basis on aggregate worldwide net sales of each product.

Since inception and through December 31, 2022, the license to the Company's intellectual property and R&D services performed by the Company are combined as a single performance obligation. Accordingly, the Company recognizes revenue for the transaction price based upon efforts or inputs to satisfy its performance obligation relative to the total expected inputs. Due to the uncertainty in the achievement of the development and regulatory milestones, the variable consideration associated with these future milestone payments has been fully constrained (excluded) from the transaction price until such time that the Company concludes that it is probable that a significant reversal of previously recognized revenue will not occur. These estimates are re-assessed at each reporting period.

In November 2022, the Company received notification from BeiGene of its intent to terminate the HER-3 ADC research program, effective January 23, 2023 (the BeiGene Notification). Prior to receipt of the BeiGene Notification, deferred revenue would have been recognized through February 2023. However, the BeiGene Notification resulted in a re-evaluation of the measure of progress for the program and the Company accelerating revenue recognition associated with the remaining deferred revenue as of the notification date.

In March 2023, the Company and BeiGene extended the initial research term for an additional two years.

NovoCodex Biopharmaceuticals Ltd. (NovoCodex)

In October 2019, the Company entered into a co-development and commercialization agreement with NovoCodex, a majority owned company of ZMC to develop and commercialize Ambrx's internally developed site-specific ADCs (the NovoCodex Agreement), and received an upfront, non-refundable, and non-creditable payment of \$2.0 million. The license to the Company's intellectual property and R&D services performed by the Company until the initial manufacturing run or technology transfer are combined as a single performance obligation. R&D services performed after the initial manufacturing run or technology transfer are considered to represent a separate performance obligation. NovoCodex may terminate the NovoCodex Agreement upon six months written notice. The Company or NovoCodex may terminate the NovoCodex Agreement for cause for safety reasons or upon other party's material breach that remains uncured after receipt of notice thereof, or upon certain bankruptcy or insolvency proceedings. The Company may also terminate the NovoCodex Agreement for cause due to NovoCodex's failure to use commercially reasonable efforts in the development and commercialization of products.

Under the terms of the NovoCodex Agreement, NovoCodex is responsible for developing and commercializing ARX305 in China while Ambrx is responsible for developing and commercializing ARX305 outside of China. NovoCodex will fund global development activities through the end of Phase 1 clinical trials. The Company is eligible to receive payments for R&D services for a minimum of one FTE based on the annual rate defined in the agreement. In addition, the Company is eligible to receive milestone payments upon achievement of certain clinical development milestone. During the fourth quarter of 2022, the Company recognized milestone revenue of \$1.0 million upon dosing of the first patient with ARX305 pursuant to the NovoCodex Agreement. The Company is also eligible to receive tiered royalties on a product-by-product basis on aggregate worldwide net sales of each product. NovoCodex is also eligible to share in a portion of ARX305 product sales outside of China. In the event the Company transfers or licenses the Phase 1 clinical data to a third party, NovoCodex is entitled to royalties on aggregate net sales of ARX305 outside of China.

Since inception and through December 31, 2022, the Company has identified two performance obligations for all promises under the NovoCodex Agreement. Accordingly, the Company recognizes revenue for the transaction price based upon efforts or inputs to satisfy its performance obligations relative to the total expected inputs. Due to the uncertainty in the achievement of the development milestones, the variable consideration associated with these future milestone payments has been fully constrained (excluded) from the transaction price until such time that the Company concludes that it is probable that a significant reversal of previously recognized revenue will not occur. These estimates are re-assessed at each reporting period.

Sino Biopharmaceutical Co., Ltd. (Sino Biopharma)

In January 2020, the Company entered into a co-development and license agreement with Sino Biopharma pursuant to which the Company (i) assigned to Sino Biopharma existing and future patent rights in the People's Republic of China (inclusive of Hong Kong, Macau and Taiwan, the Sino Territory) to ARX822 and ARX102 (each a preclinical compound) and (ii) granted exclusive rights and licenses in the Sino Territory to develop and manufacture ARX822 and ARX102 (the Sino Agreement). Sino Biopharma is solely responsible, at its own expense, for marketing, selling, offering for sale, distributing, promoting and otherwise commercializing the products in the Sino Territory. Sino Biopharma shall use commercially reasonable efforts to obtain regulatory approval for and commercialize each product. Sino Biopharma may terminate the Sino Agreement upon six months' written notice.

Under the terms of Sino Agreement, the Company received an upfront payment of \$10.0 million, which was initially subject to refund by the Company to Sino Biopharma for nonperformance; however, as of December 31, 2020, the upfront payment is no longer subject to refund. Sino Biopharma is solely responsible for costs associated with Investigational New Drug enabling activities and for providing the Company with study drug for up to 100 patients enrolled in a Phase 1 clinical trial for each of ARX822 and ARX102, if any. The Company is also eligible to receive milestone payments upon achievement of certain potential development and regulatory milestones for each program. In addition, the Company is also entitled to receive tiered royalties on a product-by-product basis on aggregate worldwide net sales of each product. With respect to each licensed product, the royalty term will terminate 12 years after the first commercial sale of such licensed product in the PRC.

Since inception and through December 31, 2022, the Company has identified one performance obligation per each preclinical compound for all promises under the agreement. Accordingly, the Company recognizes revenue for the transaction price based upon efforts or inputs to satisfy its performance obligations relative to the total expected inputs. Due to the uncertainty in the achievement of the development and regulatory milestones, the variable consideration associated with these future milestone payments has been fully constrained (excluded) from the transaction price until such time that the Company concludes that it is probable that a significant reversal of previously recognized revenue will not occur. These estimates are re-assessed at each reporting period.

Under the Sino Agreement, Sino Biopharma is solely responsible for providing the Company with study drug for the treatment of up to 100 patients, if any, enrolled in a Phase 1 clinical trial for each ARX822 and ARX102, which the Company considers to be noncash consideration. At inception of the agreement, the Company estimated the fair value of noncash consideration. Subsequent changes in the fair value of the noncash consideration, other than those attributable to a change in the form of the noncash consideration, are considered variable consideration and are included in the transaction price. Noncash consideration will be added to the transaction price to the extent a significant revenue reversal in the amount of cumulative revenue recognized will not occur when the uncertainty associated with the noncash consideration is subsequently resolved. Receipt of the study drug is not considered probable of being achieved until enrollment of either or both Phase 1 clinical trials for each of ARX822 and ARX102 commences. Any such adjustments are recorded on a cumulative catch-up basis in the period of adjustment. As of December 31, 2022, the noncash consideration has not been included in the transaction price.

Contract Assets and Liabilities

Contract balances are as follows as of December 31, (in thousands):

	2022	2021
Receivables, included in accounts receivable, net	\$ 376	\$ 1,239
Contract assets, included in prepaid expenses and other current assets	\$ —	\$ 149
Contract liabilities, included in deferred revenue, current and deferred revenue net of current portion	\$ 1,749	\$ 5,648

During the fourth quarter of 2022, the Company recognized milestone revenue of \$1.0 million from performance obligations satisfied (or partially satisfied) pursuant to the NovoCodex Agreement. During the years ended December 31, 2021, the Company did not recognize any revenue from performance obligations satisfied during the period.

A reconciliation of the beginning and ending amount of contract liabilities, which are primarily related to the combined performance obligation for the transfer of Company's license and R&D services and conducting R&D activities, which are a separate performance obligation in the Company's contracts pursuant to research plans under the agreements, was as follows for the years ended December 31, (in thousands):

	2022	2021
Beginning balance	\$ 5,648	\$ 9,731
Recognized as revenue:		
License fees	(3,442)	(3,548)
Reimbursements	(457)	(535)
Ending balance	<u>\$ 1,749</u>	<u>\$ 5,648</u>

11. Share-Based Compensation

Share-based compensation expense was as follows for the years ended December 31, (in thousands):

	2022	2021
Research and development	\$ 3,650	\$ 9,001
General and administrative	2,603	2,855
Total share-based compensation expense	<u>\$ 6,253</u>	<u>\$ 11,856</u>

On June 17, 2021, upon the closing of the Company's IPO, options to purchase 7.7 million ordinary shares became fully vested under the original vesting terms, which resulted in \$6.4 million of share-based compensation expense being recognized in the Company's consolidated statements of operations and comprehensive loss during the year ended December 31, 2021.

2016 Equity Incentive Plan

The Company granted awards under the 2016 Equity Incentive Plan (the 2016 Plan) until June 2021. The terms of the 2016 Plan provided for the grant of incentive share options within the meaning of Section 422 of the Internal Revenue Code of 1986, as amended (the Code), to the Company's employees and any parent and subsidiary corporations' employees, and for the grant of non-statutory options and restricted shares to the Company's employees, directors and consultants, and the Company's parent and subsidiary corporations' employees and consultants. The board of directors had the authority to approve the employees and other service providers to whom equity awards were granted and had the authority to determine the terms of each award, subject to the terms of the 2016 Plan, including (i) the number of ordinary shares subject to the award; (ii) when the award became exercisable; (iii) the option or share appreciation right exercise price, which needed to be at least 100% of the fair market value of the ordinary shares as of the date of grant; and (iv) the duration of the option or share appreciation right (which could not exceed 10 years). Options granted under the 2016 Plan generally are scheduled to vest over four years, subject to continued service and subject to certain acceleration of vesting provisions. In connection with the adoption of the 2021 Plan (as defined below), the Company terminated the 2016 Plan for future use and provided that no further equity awards are to be granted under the 2016 Plan. All outstanding awards under the 2016 Plan will continue to be governed by their existing terms.

2021 Equity Incentive Plan

In June 2021, the Company's board of directors adopted and the Company's shareholders approved a 2021 Equity Incentive Plan (the 2021 Plan), and the 2021 Plan became effective June 17, 2021. The 2021 Plan initially provided for the issuance of up to 56,094,909 ordinary shares. The 2021 Plan has an evergreen provision whereby the number of ordinary shares reserved for future issuance will automatically increase on January 1 of each calendar year, beginning on January 1, 2022 through January 1, 2031, in an amount equal to 5% of the total number of shares of the Company's share capital outstanding on the last day of the calendar month before the date of each automatic increase, or a lesser number of shares determined by the board of directors. The maximum number of ordinary shares that may be issued upon the exercise of incentive share options under the 2021 Plan is 200,000,000. Such shares of the Company's ordinary shares are reserved for issuance to employees, non-employee directors and

consultants of the Company. The 2021 Plan provides for the grant of incentive share options, non-incentive share options, and restricted share awards to eligible recipients. Recipients of share options shall be eligible to purchase shares of the Company's ordinary shares at an exercise price equal to no less than the (estimated) fair market value of such shares on the date of grant. The maximum term of options granted under the Plan is 10 years. Employee option grants generally vest 25% on the first anniversary of the original vesting commencement date, with the balance vesting monthly over the remaining 3 years.

Share options are generally not exercisable prior to the applicable vesting date, unless otherwise accelerated under the terms of the 2016 Plan or 2021 Plan. Although the 2021 Plan provides for options to be issued with an early exercise provision, no options, to date, have been issued with such a right.

In addition, the shares to be reserved for issuance under the 2021 Plan will also include shares subject to share options or similar awards granted under the 2016 Plan that expire or terminate without having been exercised in full and shares issued pursuant to awards granted under the Company's 2016 Plan that are forfeited to or repurchased by the Company.

On January 1, 2022, in accordance with the Company's 2021 Plan, ordinary shares available for issuance under the 2021 Plan increased by 13,506,027 ordinary shares, to 69,600,936 ordinary shares. On January 1, 2023, in accordance with the Company's 2021 Plan, ordinary shares available for issuance under the 2021 Plan increased by 13,522,762 ordinary shares, to 83,123,698 ordinary shares.

The following tables summarizes option activity for the periods presented:

	Total Options	Weighted- Average Exercise Price	Aggregate Intrinsic Value (in thousands)	Weighted- Average Remaining Contractual Life (in years)
Outstanding as of December 31, 2021	34,200,976	\$ 1.43	\$ 912	8.1
Granted	17,058,623	\$ 0.45		
Canceled	(12,143,425)	\$ 1.08		
Outstanding as of December 31, 2022	<u>39,116,174</u>	\$ 1.11	\$ 1,088	5.4
Vested and exercisable as of December 31, 2022	<u>22,083,111</u>	\$ 1.34	\$ —	4.6

As of December 31, 2021, a total of 18,950,899 vested and exercisable shares were outstanding with a weighted-average exercise price of \$1.28 per share.

There were no options exercised during the year ended December 31, 2022. During the year ended December 31, 2021, 79,212 ordinary shares were issued pursuant to option exercises for gross proceeds of \$0.1 million. The intrinsic value of options exercised during the year ended December 31, 2021 was \$0.1 million.

As of December 31, 2022, unrecognized compensation expense related to unvested share-based compensation arrangements was \$9.1 million. These costs are expected to be recognized over a weighted-average term of 3.6 years.

Ordinary Share Valuation

Prior to completion of the IPO, as there was no public market for the Company's ordinary shares, the estimated fair value of the Company's ordinary shares was historically determined by the board of directors as of the date of each option grant, with input from management, considering the most recently available third-party valuation of the Company's ordinary shares and the board of directors' assessment of additional objective and subjective factors that it believed were relevant and which may have changed from the date of the most recent third-party valuation through the date of the grant.

These third-party valuations were performed in accordance with the guidance outlined in the American Institute of Certified Public Accountants' Accounting and Valuation Guide, *Valuation of Privately-Held Company Equity Securities Issued as Compensation (AICPA Practice Aid)*. The AICPA Practice Aid identifies various available methods for allocating the enterprise value across classes or series of capital shares in determining the fair value of the Company's ordinary shares at each valuation date.

After completion of the IPO, the Company's board of directors determines the fair market value of the ordinary shares based on the closing price of the ADSs as reported on the date of grant on the primary share exchange on which the Company's ADSs are traded and as converted to the ordinary share price equivalent on the date of grant. Future expense amounts for any particular period may be affected by changes in assumptions or market conditions. The fair value of each option award is estimated on the date of grant using the BSM. The BSM requires the input of subjective assumptions, including the risk-free interest rate, the expected dividend yield of the Company's ordinary shares, the expected volatility of the price of the Company's ordinary shares, and the expected term of the option. These estimates involve inherent uncertainties and the application of management's judgment. If factors change and different assumptions are used, the Company's share-based compensation expense could be materially different in the future. These assumptions are estimated as follows:

Expected Term: The expected term represents the time period options are expected to be outstanding. For options, since the Company does not have sufficient historical experience for determining the expected term of the option awards granted, (i) it determines the expected term assumption for share options using the simplified method, which is an average of the contractual term of the option and its ordinary vesting period and (ii) for options issued out-of-the money or in-the-money, if any, the Company uses the contractual term as the expected term of the options for the expected term assumption.

Risk-Free Interest Rate: The risk-free interest rate is based on the implied yield available on U.S. Treasury zero-coupon issues with a term equivalent to that of the expected term of the share-based awards.

Expected Volatility: Expected volatility is based on the historical volatilities of industry peers as the Company has only limited trading history for its ordinary shares. The Company intends to continue to consistently apply this process using the same or a similar peer group of public companies, until a sufficient amount of historical information regarding the volatility of the price of its ordinary shares becomes available, or unless circumstances change such that the identified peer companies are no longer similar, in which case other suitable peer companies whose ordinary shares prices are publicly available would be utilized in the calculation.

Dividend Yield: The expected dividend yield is based on the Company's current expectations about its anticipated dividend policy. To date, the Company has not declared any dividends and, therefore, the Company used an expected dividend yield of zero.

The weighted-average fair value of options and ESPP (as defined below) awards issued was estimated at the date of grant using the BSM with the following weighted-average assumptions for the years ended December 31:

	Options		ESPP	
	2022	2021	2022	2021
Expected term (in years)	6.0	6.0	1.2	1.3
Risk-free interest rate	2.9%	1.0%	2.8%	0.2%
Expected volatility	82.0%	80.5%	79.2%	74.6%
Dividend yield	—	—	—	—
Weighted-average grant date fair value	\$ 0.31	\$ 1.20	\$ 0.22	\$ 0.78

Option Repricing

On January 27, 2023, the compensation committee of the board of directors of the Company approved an option repricing program (the Option Repricing) to permit the Company to reprice certain options to purchase the Company's ordinary shares held by its employees (including an officer of the Company), non-employee directors and consultants providing services as of January 27, 2023. Under the Option Repricing, eligible options with an exercise price above \$0.28 per ordinary share (or the equivalent of \$1.95 per ADS), representing an aggregate of 17,285,155 ordinary shares, or approximately 43% of the total options outstanding, were amended to reduce such exercise price to \$0.28 per ordinary share. The Option Repricing will result in additional share-based compensation expense that will be recognized in the Company's consolidated statements of operations and comprehensive loss in future periods; however, the amount of additional share-based compensation expense and the periods over which it will be recognized have not yet been determined.

2021 Employee Share Purchase Plan

In June 2021, the Company's board of directors adopted and the shareholders approved the Company's 2021 Employee Share Purchase Plan (the ESPP), which became effective on June 14, 2021. The ESPP allows eligible employees to purchase the Company's ordinary shares at a discount through payroll deductions of up to 15% of their eligible compensation, subject to any plan limitations. Initially 3,000,000 ordinary shares have been reserved for issuance under the ESPP. The ESPP has an evergreen provision whereby the number of ordinary shares reserved for future issuance will automatically increase on January 1 of each calendar year, beginning on January 1, 2022 through January 1, 2031, in an amount equal to 1% of the total number of shares of the Company's share capital outstanding on the last day of the calendar month before the date of each automatic increase, or a lesser number of shares determined by the board of directors. The offering periods generally start on December 16 and June 16 of each year and end on December 15 and June 15, respectively, approximately two years later, with each offering containing four separate six month purchase periods. The administrator may, in its discretion, modify the terms of future offerings and purchase periods. The first offering started on the Company's IPO.

On January 1, 2022, in accordance with the Company's ESPP, ordinary shares available for issuance under the ESPP increased by 2,701,205 ordinary shares, to 5,701,205 ordinary shares. On January 1, 2023, in accordance with the ESPP, ordinary shares available for issuance under the ESPP increased by 2,704,552 ordinary shares, to 8,405,757 ordinary shares.

During the year ended December 31, 2022, 334,684 ordinary shares were issued pursuant to the ESPP for gross proceeds of \$0.1 million. During the year ended December 31, 2021, 105,329 ordinary shares were issued pursuant to the ESPP for gross proceeds of \$0.1 million.

The ESPP was suspended indefinitely, effective December 16, 2022, and as of December 31, 2022 there was no unrecognized share-based compensation expense related to the ESPP.

12. Defined Contribution Plan

The Company established a defined contribution savings plan under Section 401(k) of the Internal Revenue Code (the 401(k) Plan). The 401(k) Plan covers substantially all employees who meet minimum age and service requirements and allows participants to defer a portion of their annual compensation on a pre-tax basis. Matching contributions to the 401(k) Plan may be made at the discretion of the Company's board of directors. During the years ended December 31, 2022 and 2021, the Company made discretionary contributions of \$0.4 million and \$0.3 million, to the 401(k) Plan, respectively.

13. Income Taxes

Loss before income taxes was as follows for the years ended December 31, (in thousands):

	2022	2021
U.S. operations	\$ (73,132)	\$ (61,541)
Non-U.S. operations	(2,927)	(6,746)
Loss before provision for income taxes	<u>\$ (76,059)</u>	<u>\$ (68,287)</u>

The components of the provision for income taxes was as follows for the years ended December 31, (in thousands):

	2022	2021
Current:		
U.S.	\$ —	\$ —
State and local	1	1
Foreign	1,936	—
Total current	<u>1,937</u>	<u>1</u>
Deferred:		
U.S.	—	—
Total deferred	—	—
Total provision for income taxes	<u>\$ 1,937</u>	<u>\$ 1</u>

A reconciliation of the Company's statutory income tax rate to the Company's effective income tax rate for the years ended December 31, was as follows:

	2022	2021
Income tax benefit at Cayman statutory rate	0.00%	0.00%
U.S. and non-U.S. rate differential	21.57%	19.49%
State taxes	4.77%	3.94%
R&D credits	0.73%	3.00%
Change in valuation allowance	(27.61%)	(25.79%)
Share-based compensation	(3.62%)	(0.66%)
Ambrex Shanghai reorganization	1.77%	0.00%
Other, net	(0.16%)	0.02%
Effective tax rate	<u>(2.55%)</u>	<u>(0.00%)</u>

A valuation allowance has been established as realization of deferred tax assets has not met the more likely-than-not threshold requirement. If the Company's judgment changes and it is determined that the Company will be able to realize these deferred tax assets, the tax benefits relating to any reversal of the valuation allowance on deferred tax assets as of December 31, 2022, will be accounted for as a reduction to income tax expense. During the years ended December 31, 2022 and 2021, the change in the valuation allowance from prior year was an increase of \$20.6 million and \$17.6 million, respectively.

Significant components of the Company's deferred tax assets as of December 31, are shown below (in thousands):

	2022	2021
Deferred tax assets:		
Net operating loss carryforwards	\$ 57,647	\$ 48,179
R&D credits	16,385	14,317
Capitalized R&D	8,980	—
Lease liabilities	3,110	3,662
Share-based compensation	1,219	3,223
Deferred revenues	454	1,575
Intangible assets	337	—
Other	945	1,047
Total deferred tax assets	89,077	72,003
Deferred tax liabilities:		
IPR&D	(5,436)	(5,841)
Right-of-use assets	(2,847)	(3,553)
Intangible assets	—	(2,445)
Total deferred tax liabilities	(8,283)	(11,839)
Net deferred tax assets	80,794	60,164
Less: valuation allowance	(81,674)	(61,044)
	<u>\$ (880)</u>	<u>\$ (880)</u>

As of December 31, 2022, the Company had U.S. federal, state and foreign net operating loss carryforwards of approximately \$103.5 million, \$136.2 million and \$13.7 million, respectively which will begin to expire in 2025, 2028 and 2023, respectively, unless previously utilized. Additionally, as of December 31, 2022, the Company also had U.S. federal and foreign net operating loss carryforwards of approximately \$107.1 million and \$1.7 million, respectively, which can be carried forward indefinitely. As of December 31, 2022, the Company also had U.S. federal R&D tax credit carryforwards of approximately \$12.3 million which will begin to expire in 2024 unless previously utilized. As of December 31, 2022, the Company had state tax credit carryforwards of approximately \$8.9 million, which can be carried forward indefinitely.

Pursuant to Internal Revenue Code (IRC) Sections 382 and 383, use of the Company's net operating loss and R&D income tax credit carryforwards may be limited in the event of a future cumulative change in ownership of more than 50.0% within a three-year period. The Company completed an analysis under IRC Sections 382 and 383 through June 2015 and determined the Company's U.S. net operating losses and R&D credit carryforwards may be limited due to changes in ownership in 2015. The analysis determined that substantially all net operating losses and R&D credit carryforwards could be utilized before expiration. No analysis under IRC Sections 382 and 383 has been completed for tax years 2016 through 2022. Future changes in the Company's stock ownership, which may be outside of its control, may trigger an "ownership change." In addition, future equity offerings or acquisitions that have equity as a component of the purchase price could result in an "ownership change." If an "ownership change" has occurred or does occur in the future, an annual limitation in IRC Sections 382 and 383 could result in the expiration of net operating loss and tax credit carryforwards before utilization; however, there is no tax impact as a result of the full valuation allowance on tax attributes.

The Tax Cuts and Jobs Act resulted in significant changes to the treatment of R&D expenditures under Section 174. For tax years beginning after December 31, 2021, taxpayers are required to capitalize and amortize all R&D expenditures that are paid or incurred in connection with their trade or business. Specifically, costs for U.S.-based R&D activities must be amortized over five years and costs for foreign R&D activities must be amortized over fifteen years, both using a midyear convention. During the year ended December 31, 2022, the Company capitalized \$49.5 million of R&D expenses.

As of December 31, 2022, the Company had liabilities for uncertain tax positions of \$4.7 million, of which, if recognized, \$3.3 million would not impact the Company's tax position and effective income tax rate due to a full valuation allowance. The Company's policy is to record interest and penalties related to income taxes as part of its income tax provision. As of December 31, 2022, the Company has accrued penalties of \$0.2 million related to uncertain tax positions.

A reconciliation of the beginning and ending amount of unrecognized tax benefits was as follows (in thousands):

	December 31,	
	2022	2021
Beginning balance	\$ 2,767	\$ 2,282
Additions based on tax positions related to the current year	1,958	485
Ending balance	<u>\$ 4,725</u>	<u>\$ 2,767</u>

The Company is subject to taxation in the United States, California, China, and Australia. The Company is subject to income tax examination by tax authorities in the United States in tax years 2005 to 2022 due to its net operating losses. In China, the Company is subject to income tax examinations by tax authorities for its 2018 to 2022 tax years. In Australia, the Company is subject to income tax examinations by tax authorities for its 2020 to 2022 tax years.

14. Related Party Transactions

In the ordinary course of business, the Company has related party transactions with affiliates of a noncontrolling shareholder. The following tables present the Company's activities with affiliates of the noncontrolling shareholders (in thousands):

	December 31,	
	2022	2021
Balances:		
Prepaid R&D expenses	\$ 14	\$ 55
Accounts payable	\$ 352	\$ 167
Accrued liabilities	\$ 99	\$ 250
	Years Ended December 31,	
	2022	2021
Year-to-date activity:		
Amounts paid	\$ 776	\$ 515
R&D expense recognized	\$ 146	\$ 520

Item 9. Changes in and Disagreements With Accountants on Accounting and Financial Disclosure.

None.

Item 9A. Controls and Procedures.**Conclusion Regarding the Effectiveness of Disclosure Controls and Procedures**

Our management, with the participation of our Chief Executive Officer, or CEO, and Chief Financial Officer, or CFO, has evaluated the effectiveness of our disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) as of December 31, 2022. Based on such evaluation, our CEO and CFO have concluded that, as of December 31, 2022, our disclosure controls and procedures were effective to ensure that information required to be disclosed by us in the reports that we file or submit under the Exchange Act is recorded, processed, summarized and reported, within the time periods specified in the U.S. Securities and Exchange Commission, or SEC's, rules and forms, and is accumulated and communicated to our management, including our CEO and CFO, as appropriate to allow timely decisions regarding required disclosure.

Management's Annual Report on Internal Control over Financial Reporting

Management is responsible for establishing and maintaining adequate internal control over financial reporting as such term is defined in Rule 13a-15(f) under the Exchange Act. Internal control over financial reporting is a process designed under the supervision and with the participation of our management, including our CEO and CFO, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. Our internal control over financial reporting includes those policies and procedures that (i) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of our assets; and (ii) provide reasonable assurance (a) that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles; (b) that our receipts and expenditures are being made only in accordance with authorizations of our management and directors; and (c) regarding the prevention or timely detection of the unauthorized acquisition, use or disposition of assets that could have a material effect on our financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

As of December 31, 2022, our management conducted an evaluation of the effectiveness of our internal control over financial reporting using the criteria set forth by the Committee of Sponsoring Organizations of the Treadway Commission in Internal Control - Integrated Framework (2013). Based on this evaluation, our management concluded that, as of December 31, 2022, our internal control over financial reporting was effective.

Attestation Report on Internal Control over Financial Reporting

This Annual Report does not include an attestation report of our registered public accounting firm regarding internal control over financial reporting due to an exemption established by the JOBS Act for "emerging growth companies" and because we qualify as a "non-accelerated filer" (i.e., we do not qualify as either an "accelerated filer" or a "large accelerated filer" as defined in Rule 12b-2 under the Exchange Act).

Changes in Internal Control over Financial Reporting

There were no changes in our internal control over financial reporting (as defined in Rule 13a-15(f) of the Exchange Act) that occurred during the period covered by this Annual Report that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

Inherent Limitations of Internal Controls

Our management, including our CEO and CFO, does not expect that our disclosure controls and procedures or our internal controls over financial reporting will prevent or detect all error and all fraud. A control system, no matter how well designed and operated, can provide only reasonable, not absolute, assurance that the objectives of the control system are met. Due to the inherent limitations in all control systems, no evaluation of controls can provide absolute assurance that all control issues and instances of fraud, if any, within the Company have been detected. These inherent limitations include the realities that judgments in decision-making can be faulty, and that breakdowns can occur because of a simple error or mistake. Additionally, controls can be circumvented by the individual acts of some persons, by collusion of two or more people, or by management override of the controls. The design of any system of controls also is based in part upon certain assumptions about the likelihood of future events, and there can be no assurance that any design will succeed in achieving its stated goals under all potential future conditions. Over time, controls may become inadequate because of changes in conditions, or the degree of compliance with the policies or procedures may deteriorate. Because of the inherent limitations in a cost-effective control system, misstatements due to error or fraud may occur and not be detected.

Item 9B. Other Information.

None.

Item 9C. Disclosure Regarding Foreign Jurisdictions that Prevent Inspections.

Not applicable.

PART III

Item 10. Directors, Executive Officers and Corporate Governance.

The information required by this item will be contained in our definitive proxy statement to be filed with the Securities and Exchange Commission on Schedule 14A in connection with our 2023 Annual Meeting of Shareholders ("Proxy Statement"), which is expected to be filed not later than 120 days after the end of our fiscal year ended December 31, 2022, and is incorporated by reference herein under the headings "Proposal 1 – Election of Directors," "Information Regarding the Board of Directors and Corporate Governance," "Executive Officers," and "Delinquent Section 16(a) Reports," if any.

Code of Business Conduct and Ethics

We maintain a Code of Business Conduct and Ethics that applies to all our directors, executives, employees and independent contractors of our company and our subsidiaries. This includes our principal executive officer, principal financial officer and principal accounting officer or controller, or persons performing similar functions. The full text of our Code of Business Conduct and Ethics is posted on our website at www.ambrx.com. If we make any substantive amendments to the Code of Business Conduct and Ethics or grant any waiver from a provision of the Code of Business Conduct and Ethics to any principal executive officer, principal financial officer, principal accounting officer or controller, or any person performing similar functions that are required to be disclosed pursuant to SEC rules, we will promptly disclose the nature of the amendment or waiver on our website or in a current report on Form 8-K. Information contained in, or that can be accessed through, our website is not incorporated by reference herein, and you should not consider information on our website to be part of this Annual Report.

Item 11. Executive Compensation.

The information required by this item will be contained in the Proxy Statement under the headings "Executive Compensation" and "Board of Directors and Corporate Governance – Director Compensation," and is incorporated herein by reference.

Item 12. Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters.

The information required by this item will be contained in the Proxy Statement under the headings "Security Ownership of Certain Beneficial Owners and Management" and "Executive Compensation – Equity Compensation Plan Information," and is incorporated herein by reference.

Item 13. Certain Relationships and Related Transactions, and Director Independence.

The information required by this item will be contained in the Proxy Statement under the headings "Certain Relationships and Related Party Transactions" and "Board of Directors and Corporate Governance," and is incorporated herein by reference.

Item 14. Principal Accountant Fees and Services.

The information required by this item will be contained in the Proxy Statement under the heading "Ratification of Appointment of Independent Registered Public Accounting Firm – Fees Paid to the Independent Registered Public Accounting Firm" and is incorporated herein by reference.

PART IV

Item 15. Exhibits and Financial Statement Schedules.

(a) Documents filed as part of this Annual Report

1. Consolidated Financial Statements.

The financial statements filed as part of this Annual Report are included in Part II, Item 8 of this Annual Report.

2. Financial Statement Schedules.

All schedules are omitted because they are not applicable, not required under the instructions, or the required information is shown in the financial statements or notes thereto.

(b) Exhibits Required to Be Filed by Item 601 of Regulation S-K.

Exhibit Number	Description	Incorporated by Reference Herein			
		Schedule/ Form	File No.	Exhibit	Filing Date
3.1	Amended and Restated Memorandum and Articles of Association of the Registrant, as currently in effect.	S-8	333-257264	4.2	June 22, 2021
4.1	Deposit Agreement between the Registrant and JP Morgan Chase Bank, N.A., as depositary and holders and beneficial owners of the American Depositary Shares.	S-8	333-257264	4.4	June 22, 2021
4.2	Form of American Depositary Receipt (included in Exhibit 2.1).	F-1	333-256639	4.3	May 28, 2021
4.3*	Description of Securities Registered Under Section 12 of the Exchange Act.				
4.4	Registrant's Specimen Certificate for Ordinary Shares.	F-1/A	333-256639	4.1	June 14, 2021
4.5	Shareholders Agreement, dated November 6, 2020, by and among the Registrant and the investors named therein.	F-1	333-256639	4.4	May 28, 2021
10.1†	Ambrx Biopharma Inc. Amended and Restated Share Incentive Plan (including Notice of Grant, Notice of Exercise and Option Purchase Agreement).	F-1	333-256639	10.15	May 28, 2021
10.2†	Ambrx Biopharma Inc. 2021 Equity Incentive Plan (including Forms of Option Grant Notice, Option Agreement, Notice of Exercise, Restricted Share Unit Award Notice and Restricted Share Unit Award Agreement thereunder).	F-1/A	333-256639	10.16	June 14, 2021
10.3†	Ambrx Biopharma Inc. Employee Share Purchase Program.	F-1/A	333-256639	10.17	June 14, 2021
10.4*†	Ambrx Biopharma Inc. Amended and Restated Non-Employee Director Compensation Policy.				
10.5+	License Agreement, by and between The Scripps Research Institute and the Registrant, dated as of August 26, 2003, as amended.	F-1	333-256639	10.1	May 28, 2021

Exhibit Number	Description	Incorporated by Reference Herein			
		Schedule/ Form	File No.	Exhibit	Filing Date
10.6+	Exclusive License, by and between the Regents of the University of California and the Registrant, dated as of December 16, 2009.	F-1	333-256639	10.2	May 28, 2021
10.7+	Co-Development and License Agreement, by and between Zhejiang Medicine Co. Ltd. and the Registrant, dated as of June 14, 2013.	F-1	333-256639	10.6	May 28, 2021
10.8+	Collaborative License Agreement, by and between The California Institute for Biomedical Research and the Registrant, dated as of August 23, 2013.	F-1	333-256639	10.7	May 28, 2021
10.9+	Co-Development and License Agreement, by and between NovoCodex Biopharmaceuticals Ltd. and the Registrant, dated as of October 22, 2019.	F-1	333-256639	10.9	May 28, 2021
10.10	Lease Agreement, by and between the Registrant and ARE-10933 North Torrey Pines, LLC, dated March 15, 2005.	F-1	333-256639	10.19	May 28, 2021
10.11	First Amendment to Lease Agreement, by and between the Registrant and ARE-10933 North Torrey Pines, LLC, dated May 19, 2005.	F-1	333-256639	10.20	May 28, 2021
10.12	Second Amendment to Lease Agreement, by and between the Registrant and ARE-10933 North Torrey Pines, LLC, dated December 1, 2011.	F-1	333-256639	10.21	May 28, 2021
10.13	Third Amendment to Lease Agreement, by and between the Registrant and ARE-10933 North Torrey Pines, LLC, dated July 28, 2016.	F-1	333-256639	10.22	May 28, 2021
10.14†	Form of Indemnification Agreement, by and between the Registrant and each of its executive officers and directors.	F-1	333-256639	10.11	May 28, 2021
10.15*†+	Executive Employment Agreement by and between the Registrant and Dan O'Connor, dated November 1, 2022.				
10.16†	Executive Employment Agreement by and between the Registrant and Sonja Nelson, dated June 4, 2021.	F-1/A	333-256639	10.23	June 14, 2021
10.17*†	Amendment to Executive Employment Agreement by and between the Registrant and Sonja Nelson, dated March 8, 2022.				
10.18*†+	Form of Retention Bonus Agreement by and between the Registrant and Sonja Nelson, dated March 8, 2022.				
21.1*	Subsidiaries of the Registrant.				
23.1*	Consent of Independent Registered Public Accounting Firm Deloitte & Touche LLP.				
24.1*	Power of Attorney (Contained on Signature Page to this Annual Report to Form 10-K).				

Exhibit Number	Description	Incorporated by Reference Herein			
		Schedule/ Form	File No.	Exhibit	Filing Date
31.1*	Certification of Principal Executive Officer Pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.				
31.2*	Certification of Principal Financial Officer Pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.				
32.1*#	Certification of Principal Executive Officer Pursuant to 18 U.S.C. Section 1350, as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.				
32.2*#	Certification of Principal Financial Officer Pursuant to 18 U.S.C. Section 1350, as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.				
101.INS*	Inline XBRL Instance Document – the instance document does not appear in the Interactive Data File because XBRL tags are embedded within the Inline XBRL document.				
101.SCH*	Inline XBRL Taxonomy Extension Schema Document				
101.CAL*	Inline XBRL Taxonomy Extension Calculation Linkbase Document				
101.DEF*	Inline XBRL Taxonomy Extension Definition Linkbase Document				
101.LAB*	Inline XBRL Taxonomy Extension Label Linkbase Document				
101.PRE*	Inline XBRL Taxonomy Extension Presentation Linkbase Document				
104*	Cover Page Interactive Data File (embedded within the Inline XBRL document)				

* Filed herewith.

The certifications attached as Exhibits 32.1 and 32.2 that accompany this Annual Report, are deemed furnished and not filed with the Securities and Exchange Commission and are not to be incorporated by reference into any filing of the Registrant under the Securities Act of 1933, as amended, or the Securities Exchange Act of 1934, as amended, whether made before or after the date of this Annual Report, irrespective of any general incorporation language contained in such filing.

† Indicates a management contract or any compensatory plan, contract or arrangement.

+ Pursuant to Item 601(b)(10) of Regulation S-K, certain portions of this exhibit (indicated by "[***]") have been omitted as we have determined the omitted information is the type that the Registrant customarily and actually treats as private or confidential and the omitted information is not material.

Item 16. Form 10-K Summary

None.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, as amended, the Registrant has duly caused this Annual Report on Form 10-K to be signed on its behalf by the undersigned, thereunto duly authorized.

AMBRX BIOPHARMA INC.

Date: March 30, 2023

By: /s/ Daniel J. O'Connor
Daniel J. O'Connor
President and Chief Executive Officer

POWER OF ATTORNEY

Each person whose signature appears below constitutes and appoints Daniel J. O'Connor and Sonja Nelson, and each of them, as his or her true and lawful attorney-in-fact and agent, with full power of substitution and resubstitution, for him or her and in his or her name, place and stead, in any and all capacities, to sign any and all amendments to this Annual Report on Form 10-K, and to file the same, with all exhibits thereto, and other documents in connection therewith, with the Securities and Exchange Commission, granting unto said attorneys-in-fact and agents, and each of them, full power and authority to do and perform each and every act and thing requisite and necessary to be done in connection therewith, as fully to all intents and purposes as he or she might or could do in person, hereby ratifying and confirming all that said attorneys-in-fact and agents, or any of them, or their or his substitutes, may lawfully do or cause to be done by virtue thereof.

Pursuant to the requirements of the Securities Exchange Act of 1934, as amended, this Annual Report on Form 10-K has been signed below by the following persons on behalf of the Registrant in the capacities and on the dates indicated.

Name	Title	Date
<u>/s/ Daniel J. O'Connor</u> Daniel J. O'Connor	President and Chief Executive Officer (Principal Executive Officer)	March 30, 2023
<u>/s/ Sonja Nelson</u> Sonja Nelson	Chief Financial and Operating Officer (Principal Financial and Accounting Officer)	March 30, 2023
<u>/s/ Katrin Rupalla, Ph.D.</u> Katrin Rupalla, Ph.D.	Chairperson of the Board of Directors	March 30, 2023
<u>/s/ Xiaowei Chang</u> Xiaowei Chang	Director	March 30, 2023
<u>/s/ Kate Hermans</u> Kate Hermans	Director	March 30, 2023
<u>/s/ Janet Loesberg</u> Janet Loesberg	Director	March 30, 2023
<u>/s/ Paul V. Maier</u> Paul V. Maier	Director	March 30, 2023

