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 001-40431

DAY ONE BIOPHARMACEUTICALS, INC.

(Exact name of Registrant as specified in its Charter)

Delaware	**83-2415215**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. Employer Identification No.)**
2000 Sierra Point Parkway, Suite 501 Brisbane, CA	**94005**
(Address of principal executive offices)	**(Zip Code)**

Registrant's telephone number, including area code: (650) 484-0899

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

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common Stock, par value $0.0001 per share	**DAWN**	**Nasdaq Global Select Market**

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, 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	☐	Accelerated filer	☐
Non-accelerated filer	☒	Smaller reporting company	☒
		Emerging growth company	☒

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 common equity held by non-affiliates of the Registrant, based on the closing price of the shares of common stock on June 30, 2022, was approximately $697.9 million.

The number of shares of Registrant's Common Stock outstanding as of March 1, 2023 was 73,587,094.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's Definitive Proxy Statement relating to the 2023 Annual Meeting of Shareholders are incorporated by reference into Part III of this Annual Report on Form 10-K to the extent stated herein. The Definitive Proxy Statement will be filed within 120 days of the Registrant's fiscal year ended December 31, 2022. Except with respect to information specifically incorporated by reference in this Form 10-K, the Proxy Statement is not deemed to be filed as part of this Form 10-K.

CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K contains forward-looking statements within the meaning of Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act, and section 27A of the Securities Act of 1933, as amended, or the Securities Act. All statements contained in this Annual Report other than statements of historical fact, including statements regarding our future results of operations and financial position, business strategy, market size, potential growth opportunities, nonclinical and clinical development activities, efficacy and safety profile of our product candidates, potential therapeutic benefits and economic value of our product candidates, use of net proceeds from our public offerings, our ability to maintain and recognize the benefits of certain designations received by product candidates, the timing and results of nonclinical studies and clinical trials, commercial collaboration with third parties, and our ability to recognize milestone and royalty payments from commercialization agreements, the potential impact of global business or macroeconomic conditions, including as a result of the COVID-19 pandemic, inflation and rising interest rates, and the receipt and timing of potential regulatory designations, approvals and commercialization of product candidates, are forward-looking statements. The words "believe," "may," "will," "potentially," "estimate," "continue," "anticipate," "predict," "target," "intend," "could," "would," "should," "project," "plan," "expect," and similar expressions that convey uncertainty of future events or outcomes are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

These forward-looking statements are subject to a number of risks, uncertainties and assumptions, including those described in Item 1A, "Risk Factors" and elsewhere in this Annual Report. Moreover, we operate in a very competitive and rapidly changing environment, and new risks emerge from time to time. It is not possible for our management to predict all risks, nor can we assess the impact of all factors on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in any forward-looking statements we may make. In light of these risks, uncertainties and assumptions, the forward-looking events and circumstances discussed in this Annual Report may not occur and actual results could differ materially and adversely from those anticipated or implied in the forward-looking statements.

You should not rely upon forward-looking statements as predictions of future events. Although we believe that the expectations reflected in the forward-looking statements are reasonable, we cannot guarantee that the future results, levels of activity, performance or events and circumstances reflected in the forward-looking statements will be achieved or occur. We undertake no obligation to update publicly any forward-looking statements for any reason after the date of this report to conform these statements to actual results or to changes in our expectations, except as required by law. You should read this Annual Report with the understanding that our actual future results, levels of activity, performance and events and circumstances may be materially different from what we expect.

Unless the context indicates otherwise, as used in this Annual Report on Form 10-K, the terms "Day One," "the Company," "we," "us," and "our" refer to Day One Biopharmaceuticals, Inc., a Delaware corporation, and its consolidated subsidiaries taken as a whole, unless otherwise noted. "Day One" and all product candidate names are our common law trademarks. This Annual Report contains additional trade names, trademarks and service marks of other companies, which are the property of their respective owners. We do not intend our use or display of other companies' trade names, trademarks or service marks to imply a relationship with, or endorsement or sponsorship of us by, these other companies.

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PART I

Item 1. Business.

Overview

Day One was founded to address a critical unmet need: children with cancer are being left behind in a cancer drug development revolution. Our name was inspired by the "The Day One Talk" that physicians have with patients and their families about an initial cancer diagnosis and treatment plan. We aim to re-envision cancer drug development and redefine what's possible for all people living with cancer—regardless of age—starting from Day One.

We are a clinical-stage biopharmaceutical company dedicated to developing and commercializing targeted therapies for patients of all ages with life threatening diseases. Initially, we have focused our clinical development efforts on pediatric patients living with cancer, a vulnerable population that has been underserved in the recent revolution in targeted therapeutics and immuno-oncology.

Our lead product candidate, tovorafenib (DAY101), is an oral, brain-penetrant, highly-selective type II pan-rapidly accelerated fibrosarcoma, or pan-RAF, kinase inhibitor. Tovorafenib (DAY101) has been studied in over 325 patients and has been shown to be generally well-tolerated as a monotherapy. Tovorafenib (DAY101) has demonstrated encouraging anti-tumor activity in pediatric and adult populations with specific genetic alterations that result in the over-activation of the RAS/mitogen-activated protein kinase, or MAPK, pathway leading to uncontrolled cell growth.

Tovorafenib (DAY101) has been granted Breakthrough Therapy designation by the U.S. Food and Drug Administration, or the FDA, in August 2020 for the treatment of pediatric low-grade glioma, or pLGG, based on initial results from a Phase 1 trial which showed evidence of rapid anti-tumor activity and durable responses in pLGG patients. Pediatric low-grade glioma is the most common brain tumor diagnosed in children for which there is no standard of care and for which there are no approved therapies for the majority of patients. We received Orphan Drug designation for the treatment of malignant glioma from the FDA in September 2020 and from the EU Commission for the treatment of glioma in May 2021. Additionally, the FDA granted Rare Pediatric Disease designation to tovorafenib (DAY101) for treatment of low-grade gliomas, or LGGs, harboring an activating RAF alteration in July 2021.

We have initiated and fully enrolled a pivotal Phase 2 trial, or FIREFLY-1, of tovorafenib (DAY101) as a monotherapy for pediatric patients with relapsed or progressive low-grade glioma harboring an activating BRAF alteration. The first patient was dosed in FIREFLY-1 in May 2021 and we completed enrollment in the registrational arm in May 2022. The FIREFLY-1 trial has also been expanded to: (a) include two additional study arms to enable expanded access for eligible patients now that the primary cohort has completed enrollment, and (b) evaluate the preliminary efficacy of tovorafenib (DAY101) in patients aged six months to 25 years with a relapsed or progressive extracranial solid tumor with an activating RAF fusion. We reported initial data from an interim analysis from the FIREFLY-1 trial in June 2022 and top-line data for all patients in January 2023. Topline data from January 2023 demonstrated an overall response rate, or ORR, of 64% in the 69 Response Assessment for Neuro-Oncology, or RANO, evaluable patients, comprising of 3 confirmed complete responses, or CR, and 41 partial responses, or PR (31 confirmed partial responses and 10 unconfirmed partial response, or uPR). We observed an additional 19 patients with stable disease, or SD, resulting in a clinical benefit rate of 91% (CR+ PR/uPR+ SD). Safety data, based on 77 treated patients, indicated monotherapy tovorafenib (DAY101) to be generally well-tolerated. We believe tumor reduction or stabilization is clinically meaningful for pLGG patients, as both are perceived as beneficial given the lack of approved therapies for the majority of patients. We anticipate presenting additional data from the FIREFLY-1 trial at an upcoming medical meeting in the second quarter of 2023, and reviewing key portions of the data from the study with the FDA at a pre-New Drug Application, or NDA, meeting in advance of our planned submission of an NDA in the first half of 2023.

We initiated a pivotal Phase 3 trial, or FIREFLY-2, of tovorafenib (DAY101) as a frontline therapy in pLGG in June 2022. The first patient was dosed in FIREFLY-2 in March 2023.

Our second product candidate, pimasertib, is an oral, highly-selective small molecule inhibitor of mitogen-activated protein kinase kinases 1 and 2, or MEK, a well-characterized key signaling node in the MAPK pathway. Pimasertib has been studied in more than 10 Phase 1/2 clinical trials in over 850 patients with various tumor types, both as monotherapy and in combination with standard of care therapies. Published preclinical studies indicated that pimasertib has higher central nervous system, or CNS, penetration than other MEK inhibitors.

We have initiated an open-label, multicenter, Phase 1b/2a umbrella master trial, or FIRELIGHT-1, of tovorafenib monotherapy or combination therapy, which consists of two substudies. Substudy 1 is a Phase 2 trial of tovorafenib (DAY101) as monotherapy in patients 12 years and older with RAF–altered tumors; the first patient was dosed in November 2021. Substudy 2 is a Phase 1b/2 combination trial of tovorafenib (DAY101) and pimasertib in patients 12 years and older with various MAPK-altered solid tumors; the first patient was dosed in May 2022. Simultaneous inhibition of both RAF and MEK has been shown to lead to synergistic antitumor activity in preclinical models. This combination may demonstrate enhanced anti-tumor activity in a variety of adult solid tumors driven by MAPK alterations, including NRAS mutant melanoma and lung cancers, tumors driven by Class II BRAF alterations, tumors with BRAF wild-type fusions, and tumors driven by KRAS alterations.

We believe our business development capabilities combined with our extensive experience in oncology drug development and deep ties within the research and patient advocacy communities, particularly within the pediatric setting, positions us to be a leader in identifying, acquiring and developing therapies for patients of all ages. We hold exclusive worldwide rights to tovorafenib (DAY101) and to pimasertib for all therapeutic areas subject to certain milestone and royalty payments.

Each year, approximately 15,500 children under the age of 18 in the United States and 300,000 globally are diagnosed with cancer. Moreover, cancer remains the most common cause of death by disease for children in the United States, accounting for over 1,700 deaths per year. Despite the need for safer and more effective therapies for childhood cancers, new drugs for pediatric patients are rare. Of the 117 non-hormonal oncology drugs approved by the FDA between 1997 and 2017, only six had an initial approval that included children. Generally, medicinal product testing in children is deferred until trials in adults reach late-stage clinical development. As a result, the first pediatric trials of an oncology product candidate usually initiate about six years after an initial clinical trial in adults.

In addition, the generation of large-scale molecular profiling datasets necessary to define addressable subpopulations in pediatric oncology has occurred relatively recently. Advances in our understanding of pediatric cancer biology have revealed patient populations with druggable genetic alterations. Our management team, which has significant pediatric oncology and rare diseases drug development experience, believes targeted therapies, such as tovorafenib (DAY101), have the potential to be studied in children sooner in order to address the large unmet need in pediatric cancers where new agents that address the specific genetic drivers of a tumor can meaningfully improve long-term prognosis.

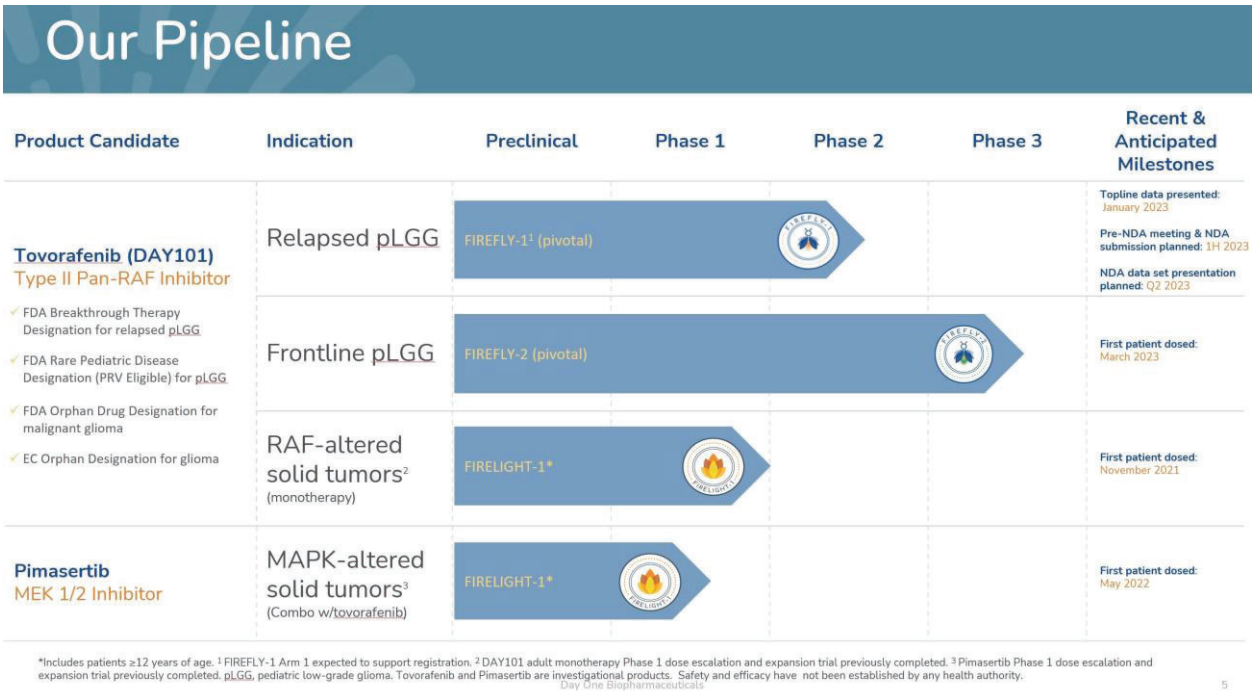
Our team's extensive capabilities and experience in pediatric oncology, and our relationships across all key stakeholders in the pediatric medical community, enable us to effectively navigate the challenges and nuances of pediatric drug development. We understand that clinical development in children cannot and should not simply be viewed as clinical development in small adults. We leverage our unique expertise to focus our initial development efforts on pediatric patients, given the potential for favorable regulatory pathways, namely Breakthrough Therapy and Orphan Drug designations.

We are driven to help children and their families fight cancer while also addressing longstanding unmet medical needs. We believe there are a number of unique advantages to developing new oncology product candidates in pediatric patients:

- **Enriched responder populations.** Many pediatric tumors are less heterogeneous and genomically more stable compared to highly heterogeneous adult tumors. Genetic alterations found in pediatric tumors are often primary driver oncogenic mutations. Directly targeting these mutations may lead to deep and sustained anti-tumor activity.
- **Ability to efficiently advance clinical development.** Global regulatory authorities have established paths for accelerated feedback on the design and execution of clinical trials in pediatrics. Furthermore, the potential to achieve proof-of-concept and regulatory approval can be obtained with relatively smaller-sized clinical trials with clear endpoints.

- **Regulatory and commercial tailwinds.** The scarcity of approved products or an established standard-of-care in pediatric oncology provides multiple opportunities to bring new therapeutics to market. Passionate patient advocacy groups and investigators have the potential to accelerate the uptake of therapies, if approved.

We seek to identify, acquire and develop product candidates that target high-value oncogenic drivers in cancers with high unmet need, with an initial focus on pediatric patients. The following table summarizes our product candidate pipeline.



Our lead product candidate, tovorafenib (DAY101), is an oral, brain-penetrant, highly-selective type II pan-RAF kinase inhibitor that inhibits both monomeric and dimeric RAF kinase. Approved BRAF products such as vemurafenib and encorafenib are referred to as type I RAF inhibitors, which only inhibit RAF monomers and are therefore limited to use in BRAF V600-altered tumors. Unlike type I RAF inhibitors, tovorafenib (DAY101) has not been shown to cause paradoxical activation in RAF wild-type cells at clinically active doses – a phenomenon wherein undesired increases in MAPK signaling can lead to renewed tumor growth. Tovorafenib's (DAY101) inhibition of both RAF monomers and dimers broadens its potential clinical application to treat an array of RAS- or RAF-altered solid tumors. Furthermore, studies have shown tovorafenib (DAY101) has higher brain penetration, distribution and exposure in comparison to other MAPK pathway inhibitors. Taken together, we believe that tovorafenib (DAY101) has the potential to be a high-impact targeted therapeutic in pLGG, where over half of pLGGs are driven by abnormal signaling due to RAF alterations.

This rationale served as the basis on which researchers at Dana-Farber Cancer Institute initiated the development of tovorafenib (DAY101) in pLGG. In a Phase 1 dose-escalation study, nine pediatric patients (<18 years of age) with relapsed pLGG were treated with tovorafenib (DAY101). Of the eight patients with RAF fusions, two achieved a complete response by Response Assessment for Neuro-Oncology, or RANO, criteria, three had a partial response, two achieved prolonged stable disease, and one experienced progressive disease as assessed by an independent radiographic review. The median time to achieve a response was 10.5 weeks, which was a notable observation given pLGG is an indolent, slow-growing tumor. In addition to the rapid anti-tumor activity observed, tovorafenib (DAY101) was also well-tolerated, which is important for achieving and maintaining long-term, durable responses in these patients. Based on these results, tovorafenib (DAY101) has been granted Breakthrough Therapy designation by the FDA for the treatment of pediatric patients with pLGG harboring an activating RAF alteration who require systemic therapy and who have either progressed following prior treatment or who have no satisfactory alternative treatment options. Tovorafenib (DAY101) received Orphan Drug designation for the treatment of

malignant glioma from the FDA in September 2020 and from the EU Commission for the treatment of glioma in May 2021. Additionally, the FDA granted Rare Pediatric Disease designation to tovorafenib (DAY101) for treatment of LGGs harboring an activating RAF alteration in July 2021.

Our second product candidate, pimasertib, is an oral, highly-selective small molecule inhibitor of mitogen-activated protein kinase kinases 1 and 2, or MEK, a well-characterized key signaling node in the MAPK pathway. Several MEK inhibitors have received regulatory approval for use in combination with type I RAF inhibitors in BRAF V600 mutant tumors. Preclinical experiments indicate that the potential benefit of combining a MEK inhibitor with a type II RAF inhibitor may be even greater due to the lack of the paradoxical effects of type II inhibitors on downstream signaling. Tovorafenib's (DAY101) ability to selectively inhibit both RAF monomers and dimers may broaden its potential clinical application in combination with MEK inhibition in solid tumors driven by RAS alterations, non-BRAF V600 mutations, and RAF fusions.

We have assembled a leadership team with a proven track record of success in building biopharmaceutical companies, and a team of drug developers with unique experience and capabilities in pediatric drug development. Our Chief Executive Officer, Jeremy Bender, Ph.D., M.B.A., brings more than 15 years of biopharmaceutical leadership experience to the company. He previously served as Vice President of Corporate Development at Gilead Sciences where he led the team responsible for Gilead's acquisitions, partnerships, and equity investments and oversaw more than 40 transactions exceeding $10 billion in upfront deal value, including the acquisition of Forty Seven, Inc. Samuel Blackman, M.D., Ph.D., our co-founder and Chief Medical Officer, is a physician-scientist trained in pediatric hematology/oncology and neuro-oncology, and has led the early clinical development of more than ten novel cancer therapeutics and was responsible for the pediatric development of dabrafenib, resulting in the first industry-sponsored pediatric oncology "basket trial." Charles York II, our Chief Operating and Financial Officer, previously served as Chief Financial Officer and Head of Corporate Development at Aeglea BioTherapeutics and has more than 20 years of strategic capital formation and leadership experience. Davy Chiodin, PharmD, our Chief Development Officer, has over 15 years of experience in both adult and pediatric oncology drug development, including the development of acalabrutinib at Acerta, now AstraZeneca, and served as Global Regulatory Leader, Pediatric Oncology, at Roche/Genentech. Mike Preigh, Ph.D., our Chief of Technology Operations, has over 25 years of experience in product development including serving as the Head of CMC at Array for over 10 years, filing over 20 Investigational New Drug Applications, or INDs, and supporting the development of marketed drugs including binimetinib and tucatinib. Jaa Roberson, our Chief People Officer, has 20 years of human resources experience across the biopharma, health insurance, and retail industries. She previously served as Head of Human Resources for Bellicum Pharmaceuticals, a clinical-stage biopharmaceutical company focused on cellular immuno-oncology. Adam Dubow, our General Counsel, has over 20 years of industry experience, most recently serving as Chief Compliance and Ethics Officer at Bristol Myers Squibb in various legal and policy roles in the United States, Asia and Europe.

Our Strategy

We have a mission-driven strategy to build a differentiated, global biopharmaceutical company through the identification, development and commercialization of therapeutics that address underserved patient populations, with an initial focus on pediatric patients. The key elements of our strategy are to:

- **Establish a leadership position in targeted oncology therapeutics for patients of all ages through our unique expertise in pediatrics.** We have built a targeted oncology company with differentiated business and clinical development capabilities. We leverage these capabilities to navigate the unique challenges and nuances of pediatric drug development. We initially focus on pediatric patients as we believe this provides a favorable pathway to approval for our product candidates. We have established trusted relationships with the pediatric oncology community, and we seek their advice on aligning our clinical development plans with the needs of the patients and their families. We believe we are a leader in this development space and to further this position, we plan to continue to consult and strategically partner with biopharmaceutical companies, academic pediatric oncologists and scientists, and patient advocacy groups to identify areas of unmet need in pediatric oncology and then acquire high-impact assets to address these underserved patients.

- **Advance our lead product candidate, tovorafenib (DAY101), through clinical development towards regulatory approval in pLGG.** We have demonstrated clinical proof-of-concept of tovorafenib (DAY101) in pediatric patients for cancers that harbor genetic alterations in RAF. Oral, once-weekly dosed tovorafenib (DAY101) was also well-tolerated in the Phase 1 trial in pLGG, which is important for achieving and maintaining long-term, durable responses in these patients. Further, tovorafenib (DAY101) received FDA Breakthrough Therapy designation for the treatment of pediatric patients with pLGG harboring an activating RAF alteration who require systemic therapy and who have either progressed following prior treatment or who have no satisfactory alternative treatment options. Tovorafenib (DAY101) also received Orphan Drug designation from the FDA for the treatment of malignant glioma. We are currently conducting a pivotal Phase 2 FIREFLY-1 trial of tovorafenib (DAY101) as a monotherapy for pediatric patients with relapsed or pLGG harboring an activating BRAF alteration. We dosed the first patient in FIREFLY-1 in May 2021 and we completed enrollment in the registrational arm in May 2022. The FIREFLY-1 trial has also been expanded to: (a) include two additional study arms to enable expanded access for eligible patients now that the primary cohort has completed enrollment, and (b) evaluate the preliminary efficacy of tovorafenib (DAY101) in patients aged six months to 25 years with a relapsed or progressive extracranial solid tumor with an activating RAF fusion. We reported initial data from an interim analysis from this trial in June 2022 and top-line data for all patients in January 2023. We initiated a pivotal Phase 3 FIREFLY-2 trial of tovorafenib (DAY101) as a frontline therapy in pLGG in the second quarter of 2022. The first patient was dosed in FIREFLY-2 in March 2023.

- **Maximize the therapeutic potential for tovorafenib (DAY101) by targeting other tumors with various unaddressed MAPK alterations, including in adults, both as a monotherapy and in combination with our second product candidate, pimasertib.** Tovorafenib (DAY101) has been dosed in over 325 patients in two adult Phase 1 open-label clinical trials—one trial investigating tovorafenib (DAY101) in monotherapy, and another in combination with other anti-cancer drugs. In both clinical trials, signs of early clinical responses emerged. Additionally, simultaneous inhibition of both RAF and MEK has been shown to lead to synergistic anti-tumor activity. We have initiated an open-label, multicenter, Phase 1b/2a FIRELIGHT-1 umbrella master trial of tovorafenib monotherapy or combination therapy, which consists of two substudies. Substudy 1 is a Phase 2 clinical trial of tovorafenib (DAY101) as monotherapy in patients 12 years and older with RAF–altered tumors; the first patient was dosed in November 2021. Substudy 2 is a Phase 1b/2 combination trial of tovorafenib (DAY101) and pimasertib in patients 12 years and older with various MAPK-altered solid tumors; the first patient was dosed in May 2022. Simultaneous inhibition of both RAF and MEK has been shown to lead to synergistic antitumor activity in preclinical models. This combination may demonstrate enhanced anti-tumor activity in a variety of adult solid tumors driven by MAPK alterations, including NRAS mutant melanoma and lung cancers, tumors driven by Class II BRAF alterations, tumors with BRAF wild-type fusions, and tumors driven by KRAS alterations.

- **Deploy our differentiated and proven business development expertise to further expand our targeted oncology pipeline for patients with large unmet medical needs.** Our team has diverse backgrounds—from academia and drug research and development, to biopharmaceutical industry and business development experience. We have a proven track record of identifying and acquiring drug candidates and programs with potentially significant commercial opportunities, including successfully in-licensing our current drug candidates, tovorafenib (DAY101) from Takeda and pimasertib from Merck KGaA, Darmstadt, Germany. We will continue to utilize our broad experience, as well as our network of trusted relationships, to source additional high-impact assets to further expand our targeted oncology pipeline.

- **Evaluate opportunities to accelerate development timelines and enhance the commercial potential of our programs in collaboration with third parties.** We own full worldwide development and commercialization rights to each of our programs subject to milestone and certain royalty payments. For additional information, see the subsection titled “Significant agreements.” In the future, we may selectively enter into collaborations where we believe there is an opportunity to accelerate the development and commercialization of our product candidates. We intend to commercialize our product candidates in key markets either alone or with partners in order to maximize the worldwide commercial potential of our programs.

Our Approach: Prioritize Pediatric Cancer and Other Areas of High Unmet Need

Our company is focused on prioritizing the clinical development of novel targeted therapeutics in pediatric patients. Historically, most pharmaceutical companies focused discovery and development efforts for new cancer therapies on adult tumor types. As a result, between 1997 and 2017, for the 126 drugs that received initial FDA approval for an oncology indication, the median time between the first-in-adult trial and the first-in-child trial was 6.5 years, regardless of whether or not the drug was a chemotherapeutic, a biologic agent, or a targeted therapeutic.

We believe that now is the right time to revisit and correct historic assumptions about pediatric oncology drug development. In doing so, we believe there are unique advantages to developing new oncology product candidates in pediatric patients, in parallel with, or even in advance of, adult indications:

- ***Enriched responder populations.*** The generation of large-scale molecular profiling datasets necessary to define addressable subpopulations in pediatric oncology has accelerated over the last decade. This has allowed scientists and drug developers to identify oncogenic drivers underlying numerous pediatric tumor types, and has revealed druggable oncogenic drivers in nearly 50% of pediatric cancers. Moreover, pediatric tumors are less heterogeneous and genomically more stable compared to highly heterogeneous adult tumors. Directly targeting these mutations may lead to deep and sustained anti-tumor activity, as demonstrated by other targeted oncology products.
- ***Ability to efficiently advance clinical development.*** Recently, global regulatory authorities have established paths for accelerated feedback on the design and execution of clinical trials in pediatrics. As part of the recent FDA Reauthorization Act, 205 relevant molecular targets were identified for pediatric cancers. In addition, new tumor-specific pediatric oncology consortia and cooperative groups have been established, allowing industry to sponsor pediatric clinical trials in the same manner as adult clinical trials. Further, the potential to achieve proof-of-concept and regulatory approval can be obtained with relatively smaller-sized clinical trials with clear endpoints.
- ***Regulatory and commercial tailwinds.*** Of the 117 non-hormonal oncology drugs approved by the FDA between 1997 and 2017, only six had an initial approval that included children. The scarcity of approved products or an established standard of care, particularly in relapsed disease in pediatric oncology, provides multiple opportunities to bring new therapeutics to market. Passionate patient advocacy groups and investigators have the potential to accelerate the uptake of therapies, if approved.

Our company is uniquely positioned to deliver much-needed targeted therapeutics to pediatric oncology patients. We have extensive capabilities and experience with these patients, and our trusted relationships across all key stakeholders in the pediatric medical community enable us to effectively navigate the challenges and nuances of pediatric drug development. Key advantages that allow us to successfully identify and execute on opportunities in pediatric oncology include:

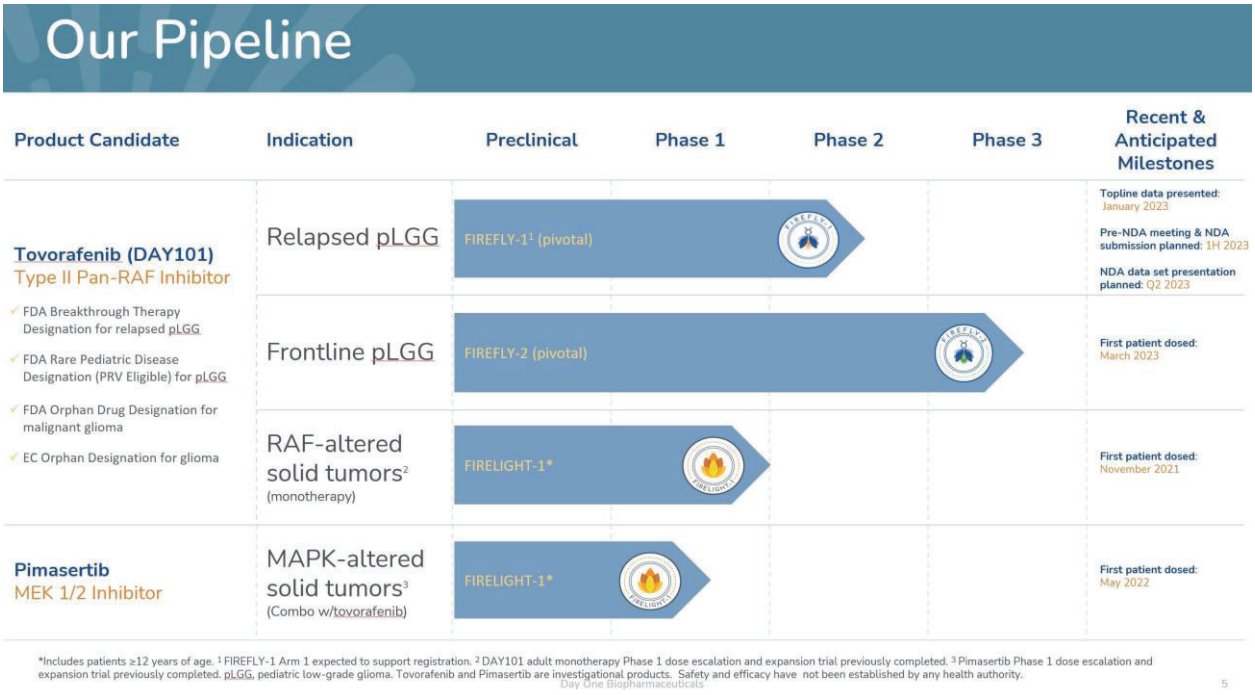
- ***Aggregation of insights from a diverse group of key stakeholders to identify attractive development opportunities based on patient need and underlying biology.*** The broad scientific expertise of our team and within our trusted global network of scientific advisors, allows us to focus and identify areas of cancer biology that are relevant to children, adolescents and adults. For instance, the BRAF wild-type gene fusions that are the most common BRAF alteration in pLGG have been shown to be oncogenic in several adult solid tumor types, and may be addressable with tovorafenib (DAY101) as monotherapy, or in combination with a MEK inhibitor, such as pimasertib.

- ***Business development opportunities enabled by key relationships and a dedication to prioritize pediatric drug development.*** We believe we are routinely among the first to evaluate emerging clinical and preclinical data that could underlie new drug development programs in pediatric oncology indications as a result of our deep roots and extensive network within the pediatric oncology research community. For example, we were made aware of the opportunity to in-license tovorafenib (DAY101) from Takeda, and were able to rapidly gain insights into the emerging data due to our relationships within the pediatric oncology investigational medicine community including but not limited to the Dana-Farber Cancer Institute, and the Pacific Pediatric Neuro-Oncology Consortium, or PNOC, and members of the Low Grade Glioma in Childhood, or LOGGIC, Consortium based at Hopp Children's Cancer Center in Heidelberg, Germany.
- ***Organizational focus on overcoming the historical challenges to executing pediatric clinical trials.*** We understand that clinical development in children is unique and must be approached as such. Clinical development in children is not the same as clinical development in adults and requires a deep organizational focus to address the needs of families, pediatric investigators, patient advocacy communities, and the patients. We have established trusted relationships with the pediatric oncology community globally, including major cooperative groups and disease-specific consortia, and we seek their advice on aligning our clinical development plans with the needs of the patients and their families. Our team is deeply experienced in designing modern, novel, and capital-efficient clinical development plans, as well as in obtaining early regulatory alignment on those plans—similar to an ultra-rare disease model. For example, as a result of the lack of any standard-of-care or approved therapies for the majority of pLGG patients, we believe that our pivotal Phase 2 trial is expected to provide a sufficient dataset to support approval based on preliminary discussions with regulatory agencies.

These capabilities will enable us to develop targeted therapeutics from which pediatric patients can benefit. We believe we are a leader in this development space and to further this position, we plan to continue to consult and strategically partner with biopharmaceutical companies, academic pediatric oncologists and scientists, and patient advocacy groups to identify areas of unmet need in pediatric oncology and then acquire high-impact assets to address these underserved patients. While our initial focus is on pediatric patients, we also pursue the clinical development of targeted therapies with equivalent intensity for adult populations.

Our Product Candidates

We seek to identify, acquire and develop product candidates that target high-value oncogenic drivers in cancers with high unmet need, with an initial focus on pediatric patients. Although our clinical development begins by leveraging our unique expertise in the pediatric oncology setting, we are committed to advancing targeted therapies for adult cancer patients with equivalent intensity. The following table summarizes our product candidate pipeline.



Tovorafenib (DAY101)

Our lead product candidate, tovorafenib (DAY101), is an oral, brain-penetrant, highly-selective type II pan-RAF kinase inhibitor. Tovorafenib (DAY101) has been studied in over 325 patients, and as a monotherapy demonstrated good tolerability and encouraging anti-tumor activity in pediatric and adult populations with specific MAPK pathway-alterations. We have initiated and fully enrolled a pivotal Phase 2 FIREFLY-1 trial of tovorafenib (DAY101) as a monotherapy for pLGG, the most common brain tumor diagnosed in children, for which there are no approved therapies and no recognized standard of care for the majority of patients. The FIREFLY-1 trial has also been expanded to: (a) include two additional study arms to enable expanded access for eligible patients now that the primary cohort has completed enrollment, and (b) evaluate the preliminary efficacy of tovorafenib (DAY101) in patients aged six months to 25 years with a relapsed or progressive extracranial solid tumor with an activating RAF fusion. We reported initial data from an interim analysis from this trial in June 2022 and top-line data for all patients in January 2023. We anticipate presenting additional data from the FIREFLY-1 trial at an upcoming medical meeting in the second quarter of 2023, and reviewing key portions of the data from the study with the FDA, at a pre-NDA meeting in advance of our planned submission of an NDA in the first half of 2023. As is generally customary in our industry, we also anticipate reporting our data at a medical or scientific meeting in 2023. Tovorafenib (DAY101) has been granted Breakthrough Therapy designation by the FDA for the treatment of pLGG based on initial results from a Phase 1 trial which showed evidence of rapid anti-tumor activity and durable responses in pLGG patients. We are also studying tovorafenib (DAY101) alone in combination with other agents that target key signaling nodes in the MAPK pathway in patient populations where various RAS and RAF alterations are believed to play an important role in driving disease.

RAF kinase drives cell proliferation and carcinogenesis

Cell functions such as growth, survival and differentiation are regulated by cascades of signaling events of which RAF kinase is a critical component. RAF is a protein kinase that is normally activated by RAS, a protein that transmits activating signals from extracellular receptors to RAF. Activation of RAF then leads to the activation of MEK kinase and the downstream MAPK pathway. Genetic alterations that result in overactivation of the pathway, such as RAS or RAF alterations, have long been characterized as oncogenic.

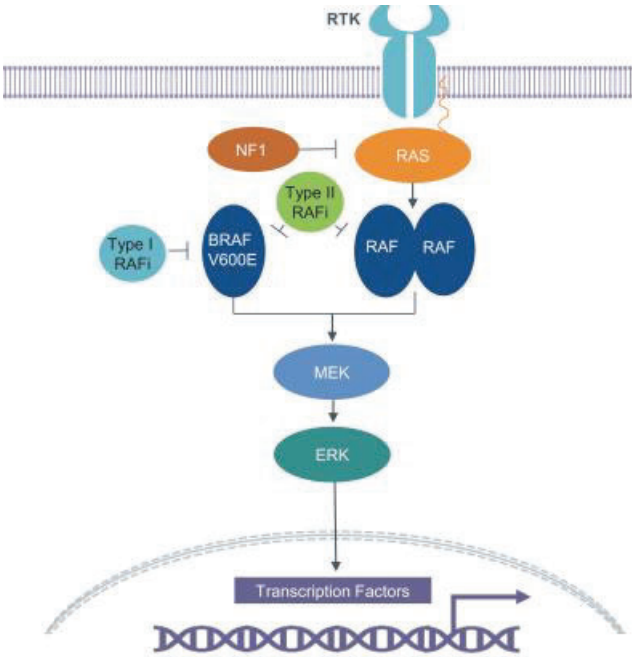


Figure 1. RAF kinases (ARAF, BRAF, CRAF) are critical components of the MAPK pathway. BRAF V600E can signal as a monomer and is sensitive to type I and type II RAF inhibitors. Wild-type RAF dimers are only sensitive to type II RAF inhibitors. Modified from: Solit and Rosen, Cancer Discover, 2014.

One of the most frequently altered genes in this pathway is BRAF, one of three RAF genes in human cells and the form of RAF most easily activated by RAS. The majority of alterations in BRAF are mutations known as V600. Mutations in V600 transform non-mutant or wild-type BRAF into a form of BRAF that has increased signaling activity and is no longer dependent on RAS for activation. The abundance of V600 mutant BRAF and its central role in tumor growth have made it a focus of historical drug discovery efforts.

Another class of important oncogenic BRAF alterations are BRAF wild-type gene fusions. Gene fusions involving BRAF occur through intra- or inter-chromosomal rearrangements in which genes for unrelated proteins are physically joined together resulting in the synthesis of a chimeric protein. BRAF consists of a regulatory domain which modulates the activity of BRAF, and a catalytic kinase domain which then activates downstream signaling to promote cell growth. In BRAF fusions, the regulatory domain of BRAF is replaced with a different sequence, allowing BRAF to signal independent of RAS activation. This uncoupling of the regulatory and catalytic domains of BRAF has important consequences: the resultant novel oncogene is both aberrantly expressed and it also exhibits constitutive, or always-on, activation of the kinase domain. This kinase activity can result in the activation of downstream oncogenic signaling, exacerbating tumor growth. BRAF gene fusions have been observed in patients with prostate cancer, melanoma, radiation-induced thyroid cancer, and pLGG.

Three BRAF inhibitors have been approved by the FDA for the treatment of certain solid tumors containing only BRAF V600E or V600K mutations, including melanoma, non-small cell lung cancer, anaplastic thyroid cancer, and colorectal cancer. These first-generation BRAF inhibitors, known more generally as type I RAF inhibitors, are vemurafenib, marketed as Zelboraf® by Genentech; dabrafenib, marketed as Tafinlar® by Novartis; and encorafenib, marketed as Braftovi® by Pfizer. However, despite initial clinical responses to monotherapy type 1 RAF inhibitors, most patients relapse within one year following the initiation of treatment.

One way by which resistance develops to type I RAF inhibitors is related to the mechanism of normal RAF activation in cells. In contrast to the constitutively active V600E or V600K variant, which is active as a monomer, normal RAF function requires formation of dimers of RAF. Approved inhibitors of V600E/K BRAF do not block the activity of RAF dimers or other non-V600 BRAF mutations. In fact, the binding of some of these inhibitors to V600E/K BRAF can stimulate the formation of dimers, thereby causing paradoxical activation (undesired increases in MAP kinase signaling) in RAF wild-type cells – a phenomenon which could potentially lead to renewed tumor growth. Paradoxical activation of wild-type RAF also occurs in non-tumor tissue. This leads to a common adverse event associated with these agents—the development of proliferative pre-malignant and malignant skin lesions. In order to avoid resistance and paradoxical activation, in many instances type I RAF inhibitors need to be given in combination with MEK inhibitors, but again only to patients with BRAF V600E/K mutations.

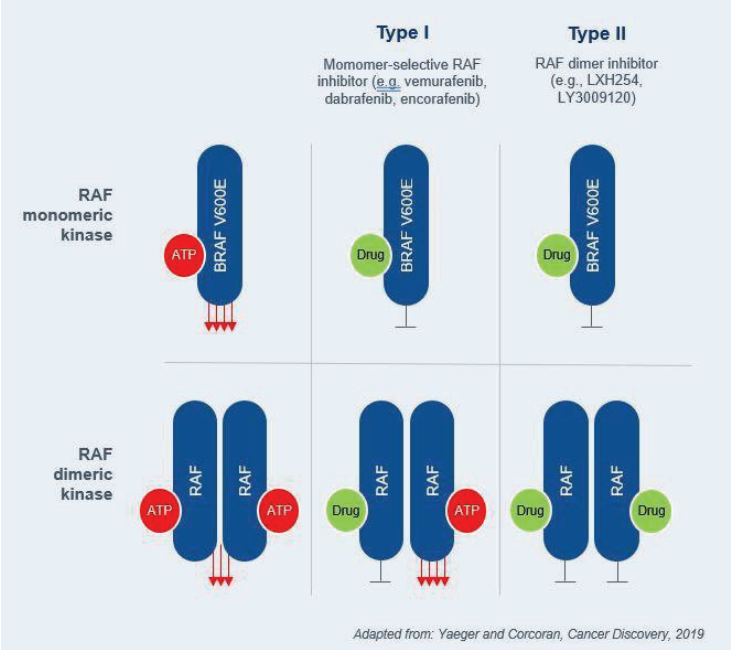


Figure 2. Schema showing the effect of different RAF inhibitors on monomeric RAF kinases (i.e., BRAF V600E; top section) or dimeric RAF kinases (bottom section). ERK activation is strongly activated downstream of BRAF V600E, even more so than seen for dimeric RAF kinase signaling. Monomer-selective type I RAF inhibitors bind to the ATP site in BRAF monomers and inhibit downstream signaling. In RAF dimeric kinases, binding of drug inhibits the bound RAF protomer, but leads to a conformational change in the other protomer in the dimer pair and strong transactivation of this protomer, leading to overall increased ERK activation (paradoxical activation). Type II RAF inhibitors are able to bind to mutant RAF monomers and dimers at equipotent doses and therefore can inhibit mutant RAF monomers and dimers at the same dose. Adapted from Yaeger and Corcoran, Cancer Discovery, 2019.

Type I RAF inhibitors that target V600E/K alterations are not able to inhibit the wild-type RAF kinase domains in KIAA1549-BRAF gene fusions and are thus unable to effectively inhibit the overactive signaling that results from this fusion. Furthermore, because of the potential for paradoxical activation, these RAF inhibitors are contraindicated in patients with BRAF gene fusions.

DAY101's (tovorafenib) mechanism of action

Tovorafenib (DAY101) is a selective, small molecule RAF inhibitor that can block the activity of multiple forms of RAF including wild-type RAF, BRAF and CRAF fusion proteins, and variants that function as dimers (Class II mutations), as well as variants such as BRAF V600E and non-V600E mutations that function as monomers (Class I mutations). Tovorafenib (DAY101) is known as a type II RAF inhibitor as it's designed to inhibit both monomeric and dimeric RAF kinase. DAY101's (tovorafenib) inhibition of both RAF monomers and dimers broadens its potential clinical application to treat an array of RAF-altered tumors.

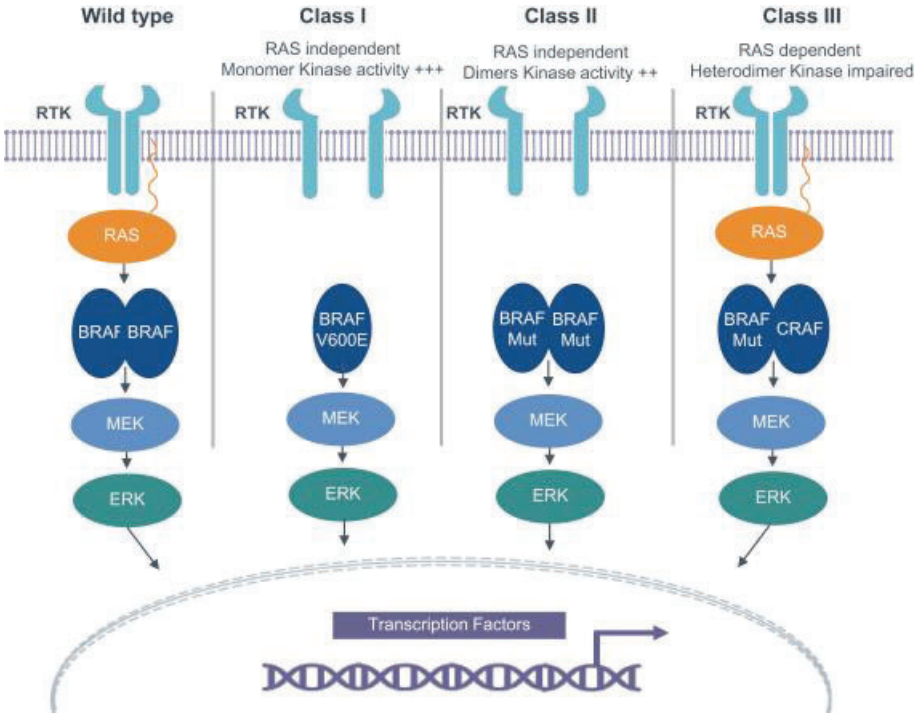


Figure 3. Signaling pathways in different classes of BRAF mutations. BRAF V600 mutations (Class I) are independent of RAS signaling and work as monomers. BRAF non-V600 Class II mutations are also independent of RAS but signal as constitutive dimers. The Class II mutations include BRAF wild-type fusions. Non-V600 Class III BRAF mutations have low or no kinase activity and depend on RAS activation acting as amplifiers of the RAS signaling pathway. Tovorafenib (DAY101) inhibits Class I and Class II RAF alterations, including BRAF wild-type fusions and non-V600E/K variations. Modified from Fontana and Valeri, Clinical Cancer Research, 2019.

Pediatric low-grade glioma disease and treatment overview

Pediatric low-grade glioma is the most common brain tumor diagnosed in children, accounting for 30%-50% of all central nervous system tumors. For the most part, these tumors are slow-growing, chronic, and relentless. While malignant transformation and dissemination of pLGGs are rare there are many long-term consequences of the disease. The growth of pLGG is highly morbid as pLGG tumors are space-occupying lesions that have the potential to compress critical neurovascular structures in the brain. Symptoms can vary from patient to patient depending on the location of the tumor and the amount of pressure it exerts on surrounding tissues. These symptoms can include headaches, nausea, vomiting, lethargy, sixth cranial nerve palsies, seizures and behavioral changes, depending on tumor location. The majority of children with pLGG are long-term survivors and live into adulthood; however, survivors of pediatric glioma often suffer long-lasting functional, neurologic, and endocrine complications from their disease and/or treatment. These patients require more effective treatment strategies that minimize long-term morbidity and treatment-associated toxicity.

Patients with pLGG have historically been treated with surgery, radiation, and chemotherapy. While surgical resection of pLGG is associated with 10-year overall survival rates of 90% or more, the majority of children are unable to undergo complete resection, a procedure which can be associated in some instances with significant and long-lasting morbidity. Incompletely resected or unresectable pLGG is associated with a high rate of disease progression or recurrence. Patients with subtotal resections have a 10-year progression-free survival of only 55%. Although more modern radiation therapy modalities have been shown to lead to improvements in progression free survival, radiotherapy is historically associated with a risk of significant decline in neurocognitive outcomes in younger children, as well as the risk of endocrine dysfunction, secondary malignancy, and an increased risk of stroke. As a result, even modern radiation therapy techniques continue to be reserved for use when all other therapies have failed.

Most patients with progressive pLGG requiring initial systemic therapy are treated with combination chemotherapy such carboplatin/vincristine or, in certain countries, vinblastine as a single-agent. Results from the largest randomized Phase 3 study for children with newly diagnosed pLGG showed a 5-year event-free survival of 47% for vincristine/carboplatin. Outcomes for a subgroup of pLGG patients not associated with neurofibromatosis, which included those with BRAF alterations, were inferior, showing a 5-year event-free survival of 39%. Of note, the overall response rate to chemotherapy in newly diagnosed pLGG patients was 30%-35%. In addition to chemotherapy's efficacy limitations, treatment-related morbidity was significant, with more than 95% of patients having experienced at least one Grade 3 or Grade 4 adverse event. There is no standard-of-care therapy for patients whose tumors progress following the failure of these combinations, and no targeted therapeutics have been approved for this patient population.

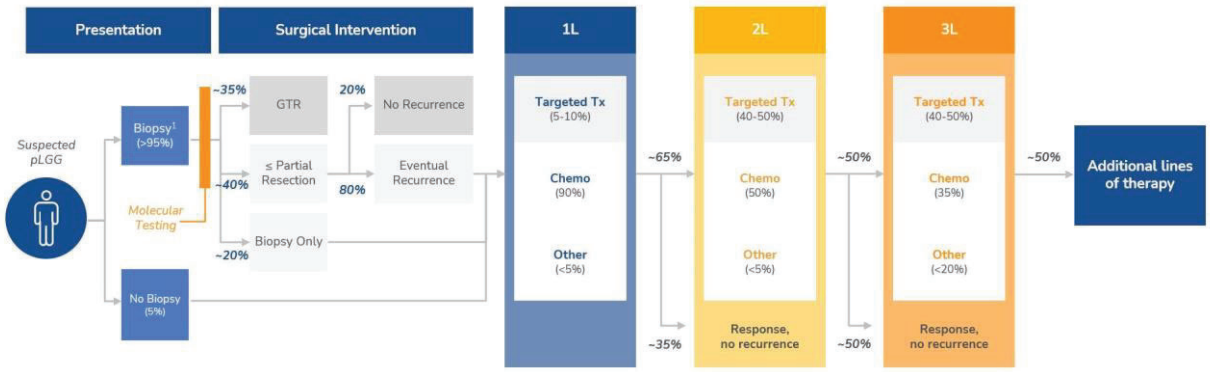


Figure 4. Treatment paradigm for pLGG.

Because many pLGGs undergo senescence when patient ages reach their 20s, the goal of therapy is to maximize tumor control while minimizing treatment-associated toxicities from surgery, chemotherapy, and radiation. As a result, a large number of pLGG patients will undergo multiple lines of systemic therapy over the course of their disease.

Based on incidence results published in academic journals, we estimate that approximately 1,100 patients under the age of 25 are newly diagnosed with BRAF-altered pLGG every year. We estimate that the SEER prevalence in the United States for patients under the age of 25 as of January 1, 2017 was approximately 130,000 patients presenting brain and other nervous system tumors, of which 26,000 presented BRAF-altered pLGG.

Over the last decade, it has been found that between 50% and 60% of pLGGs are driven by abnormal signaling due to alterations in RAF, approximately 85% to 90% of which are a gene fusion known as KIAA1549-BRAF. This gene alteration results in the expression of a wild-type BRAF catalytic domain without its normal regulatory domain, thereby rendering constitutively active BRAF activity. In addition, between 5% and 17% of children with pLGGs have tumors with a BRAF V600E activating mutation. No targeted therapeutics have been approved for the treatment of pLGG, and there are currently no therapies approved for pediatric patients with RAF alterations—the largest subset of patients with pLGG.

Indirect targeting of KIAA1549-BRAF gene alterations is possible with the off-label use of approved drugs that target components of the downstream RAF signaling pathway, such as with therapies that target MEK. Targeting of BRAF V600E mutations is possible with the off-label use of type I RAF inhibitors that have been approved for adult indications such as melanoma. An investigator-sponsored clinical trials of the MEK inhibitor selumetinib has recently been published. This study included 25 patients with either a KIAA1549-BRAF fusion or a BRAF V600E mutation. Nine of 25 patients achieved a sustained partial response. Sixteen percent of patients had Grade 3 elevation on creatine phosphokinase, and 8% of patients had Grade 3 acneiform rash. Ten of 25 patients (40%) required a dose reduction due to treatment-related adverse events and one (4%) required two dose reductions. Similarly, a retrospective analysis of the MEK inhibitor trametinib in 18 patients was recently published, showing six partial responses, two minor responses, and 10 stable diseases as best overall responses. Treatment-related adverse events occurred in 89% of patients, including 44% with severe (Grade 3 or Grade 4) adverse events, which required dose reduction in 33% of patients and discontinuation in 11% of patients. An industry-sponsored Phase 1/2a study of dabrafenib in 110 pLGG patients with BRAF V600E mutations was recently published, showing a confirmed objective response rate, or ORR, of 47%, which included one complete response and 13 partial responses, with a median duration of response of 26 months. Grade 3 or 4 treatment-related adverse events were reported in 28% of patients, and included new or increased size of melanocytic nevi in 25% of patients but no cases of squamous cell carcinoma. Ten patients (31%) had adverse events that led to dose interruptions or reductions, and 6% of patients had adverse events that led to treatment discontinuation. Finally, an industry-sponsored Phase 2 study of either trametinib monotherapy or dabrafenib/trametinib in combination in patients with BRAF V600 mutant relapsed/refractory pLGG was recently published. This study showed an independently assessed objective response rate of 15% for monotherapy trametinib (n=13) and 25% (n=36) for the combination. 25% of patients receiving the combination had serious adverse events. 16% of patients had adverse events leading to dose-reduction while 44% had an adverse event leading to dose interruption, and 11% had adverse events leading to drug discontinuation. The most common adverse events were pyrexia (50%), dry skin (41%), acneiform rash (39%), fatigue (39%), and rash (36%).

Taken together, these investigations have shown some of the existing MEK and type I RAF inhibitors have been shown, in small trials, to have activity in pLGG, but are accompanied by frequent Grade 3 or Grade 4 adverse events, and the need for dose reduction or interruption. With the exception of the combination of dabrafenib/trametinib for patients >6 years of age with relapsed/progressive tumors bearing a BRAF V600E/K mutation, there have been no agents approved for use in this population and as such, are only available via clinical trials or off-label prescription. Off-label use, while common in the pediatric oncology setting, is recognized to be an inferior approach as it exposes children to potential risks without the associated safeguards that accompany comprehensive clinical development activities, such as long-term safety monitoring and pharmacovigilance activities. We believe that the intentional development of a specifically-targeted, brain-penetrant therapy for pLGG is essential to improve outcomes for these patients, particularly those with BRAF fusions, and patients with BRAF V600E mutations who are either <6 years of age or who have progressed on, or cannot tolerate, combined Type I RAF/MEK inhibition.

Clinical trial results for pLGG

Tovorafenib (DAY101) is currently being evaluated in an ongoing investigator-initiated, multi-center study (PNOC014, NCT03429803) in patients with relapsed/refractory gliomas (high- and low-grade) and other tumors that is being conducted by Dana-Farber Cancer Institute in collaboration with PNOC. The trial remains open but is closed to new patient accrual. As of November 2022, a total of 44 patients had been enrolled in Part B of this Phase 1 dose-escalation trial (9 patients in Part A, 35 patients in Part B), which was conducted at multiple institutions within the PNOC network. Once-weekly tovorafenib (DAY101) at doses as high as 420 mg/m^2/week were well-tolerated in patients ≥ 1.5m^2, while doses as high as 530 mg/m^2/week were found to be well-tolerated in patients <

1.5m^2. Data was recently presented at the 2022 Society for Neuro-Oncology meeting for the 35 patients studied in Part B. For this group, there were two complete responses, seven partial responses, fifteen patients with stable disease and eight patients who had progressive disease. There were six dose limiting toxicities, all at 530 mg/m^2/week, all Grade 3, and five known side effects (two fatigue, three rash, one menorrhagia).

As shown in Figure 5 below, the Phase 1 trial, which initially started in February 2018, was designed to determine maximum tolerated dose, or MTD, in pediatric patients. Part A of this trial was an initial dose-escalation of tovorafenib (DAY101) as monotherapy that utilized a 3+3 design. The starting dose of 280 mg/m2 was 80% of the adult recommended phase 2 dose, or RP2D, of 600 mg orally once weekly, adjusted for body surface area. Patients enrolled in this trial were treated for a period of up to two years. The trial was amended in December 2019 to continue dose escalation, using an adaptive design, until either dose limiting toxicities, or DLTs, or the MTD was observed.

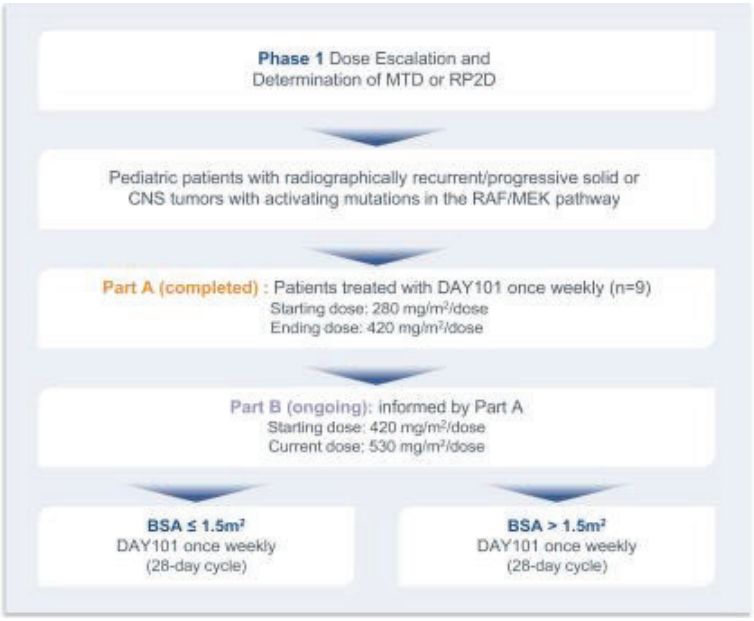


Figure 5. Design of the Phase 1 trial of tovorafenib (DAY101) in pLGG.

Tovorafenib (DAY101) was studied in a Phase 1 investigator-initiated trial (PNOC014; NCT03429803) in which it was administered once weekly as oral immediate release tablets to patients with relapsed/refractory tumors with LGGs and other RAS/RAF/MEK/ERK pathway-activated tumors. Data from Part A of this study was presented in November 2020 in which tovorafenib was evaluated at three different dose levels: 280 mg/m2, 350 mg/m2, and 420 mg/m2, with three patients at each dose level. Tovorafenib was well tolerated at all doses tested with no dose reductions or interruptions in patients receiving doses of 420 mg/m2 or below. None of these patients experienced a DLT. The vast majority of treatment emergent adverse events, or TEAEs, were Grade 1 or 2. No ophthalmologic or cardiac adverse events were observed. The most frequently reported TEAEs across all dose cohorts in Part A were all Grade 1 or 2 in severity and included rash (89%), graying of the hair (achromotrichia) (78%), moles (nevus) (78%), anemia (67%), and itching (pruritis) (67%). One patient experienced a single Grade 3 adverse event (increased creatinine phosphokinase), and there were no Grade 4 adverse events reported. These side effects were found to be reversible and manageable.

While 420 mg/m2 was initially considered the RP2D because of anti-tumor activity observed at all dose levels in Part A, dose escalation was continued in Part B of this study an attempt to determine a MTD. Upon resumption of the dose-escalation portion in Part B of this trial, the dose escalation was split between two subgroups, based on body surface area, to account for the possibility that at dose levels of 530mg/m2 or higher there might be larger children that may exceed the adult MTD at a given dose level, while smaller children may not. Data from Part B of this study was presented in November of 2022. Thirty-five additional patients were enrolled in Part B

PNOC014: 21 patients with gliomas bearing a KIAA1549:BRAF fusion, nine patients with tumors bearing a BRAFV600E mutation, four with a novel RAF- and one with an FGFR1-altered tumor. Histologically, cohort included 30 LGGs, four high grade gliomas and one soft tissue sarcoma. There were six DLTs: three in each body surface area, or BSA, subgroup, all at 530 mg/m2/dose, all Grade 3, and five known side effects (two fatigue, three rash, one menorrhagia). Across these 35 patients, oral weekly tovorafenib (DAY101) was well tolerated. While the TITE-BOIN continuous reassessment model recommended 530 mg/m2/dose per os, or PO, weekly for patients with BSA < 1.5m2 and 420 mg/m2/dose PO weekly for patients with BSA >1.5m2, the probability of a DLT for patients with a BSA < 1.5m2 was found to be nearly 20%. As such, 420 mg/m2/dose PO weekly was selected as the dose for the pivotal Phase 2 FIREFLY-1 and pivotal Phase 3 FIREFLY-2 studies.

Overall, data from the now-completed Part A, where the patients received up to two years of continuous treatment, supported by data from Part B, indicate that the tolerability profile of tovorafenib (DAY101) at 420mg/m2 supports the potential for chronic long-term usage of tovorafenib (DAY101).

A standard objective measure of efficacy accepted by the FDA for brain tumors is a set of radiographic measurement criteria called RANO. RANO criteria take into account various measures of tumor dimensions to track response to therapy or disease progression. Data from patients in Part A of PNOC014 were reviewed by an independent neuro-radiologist using RANO criteria. Eight of the nine patients had a pLGG with a RAF fusion (seven with a KIAA1549-BRAF fusion and one with an SRGAP3-CRAF fusion), while one patient had a loss-of-function mutation in the gene for neurofibromatosis 1, or NF1. As seen in Figure 6 below, five of the eight patients with a RAF fusion had either a complete response or a partial response per RANO criteria, defined as 50% decrease, compared with baseline; the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks. Two of eight patients with a RAF fusion had prolonged stable disease. One patient with a RAF fusion did not respond to tovorafenib (DAY101). The one patient with an NF1-associated pLGG did not respond to tovorafenib (DAY101). Radiologic responses using exploratory imaging measures such as volumetric image analysis or the recently published, but clinically unvalidated, RAPNO Criteria, or Response Assessment for Pediatric Neuro-Oncology, which we believe were largely consistent with the RANO scores.

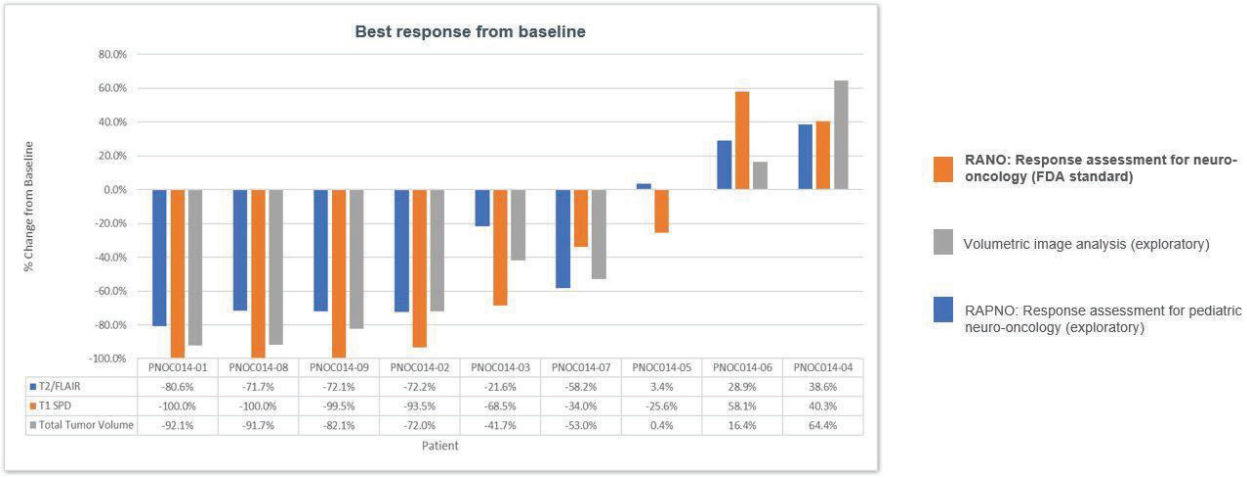


Figure 6. Five of nine patients in the tovorafenib (DAY101) Phase 1 trial in pLGG had a complete (100% reduction) or partial response (>50% reduction in the bi-dimensional measurement of the tumor).

In addition to evaluating responses on-treatment, target lesions were identified in each patient during screening and baseline growth kinetics calculated from prior radiologic images. For eight of the nine patients, there was a documented history of tumor growth prior to trial enrollment. As shown in Figure 7, shrinkage in lesion size was observed in six of nine patients in the first radiologic images obtained after initiation of tovorafenib (DAY101) dosing. The median time to response was 10.5 weeks, which is a notable observation given pLGG is an indolent, slow-growing tumor. Two patients achieved a complete response that was maintained throughout the dosing period of up to two years. Three patients had a partial response, two achieved prolonged stable disease, and two did not achieve a response. The trial allowed for treatment for maximum duration of two years.

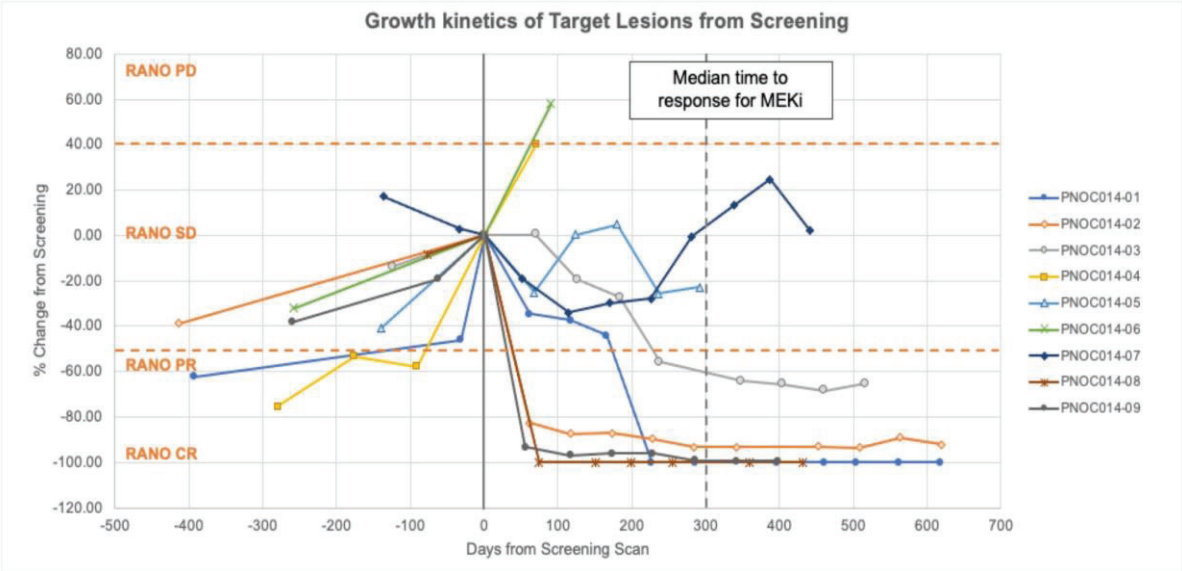


Figure 7. Individual patient responses in the tovorafenib (DAY101) Phase 1 trial in pLGG.

Based on the results from Part A of PNOC014, tovorafenib (DAY101) has been granted Breakthrough Therapy designation by the FDA for the treatment of pediatric patients with pLGG harboring an activating RAF alteration who require systemic therapy and who have either progressed following prior treatment or who have no satisfactory alternative treatment options. Tovorafenib (DAY101) also received Orphan Drug designation from the FDA for the treatment of malignant glioma.

Clinical development plan for pLGG

We have initiated a pivotal Phase 2 FIREFLY-1 trial of tovorafenib (DAY101) in pediatric patients aged six months to 25 years with relapsed or progressive pLGGs harboring an activating BRAF alteration, such as a KIAA1549-BRAF fusion or a BRAF activating mutation, such as V600E. This is an open-label, global registrational, single-arm trial of oral tovorafenib (DAY101) administered once weekly at a dose of 420 mg/m2. Patients will continue on tovorafenib (DAY101) until radiographic evidence of disease progression by RANO criteria as determined by treating investigator, unacceptable toxicity, patient withdrawal of consent, or death. The first patient was dosed in FIREFLY-1 in May 2021 and we completed enrollment in the registrational arm in May 2022. The FIREFLY-1 trial has also been expanded to: (a) include two additional study arms to enable expanded access for eligible patients now that the primary cohort has completed enrollment, and (b) evaluate the preliminary efficacy of tovorafenib (DAY101) in patients aged six months to 25 years with a relapsed or progressive extracranial solid tumor with an activating RAF fusion. We anticipate that this trial will generate a dataset that, in combination with the existing safety database, will have the potential to serve as the basis for regulatory approval. We anticipate the primary endpoint will be overall response rate, defined as the proportion of patients with best overall confirmed response rate (complete response and partial response based on the RANO criteria), as determined by independent

review. Secondary and exploratory endpoints include the overall response rate based on RAPNO and volumetric analyses, event free survival, safety, functional outcomes, and quality of life measures.

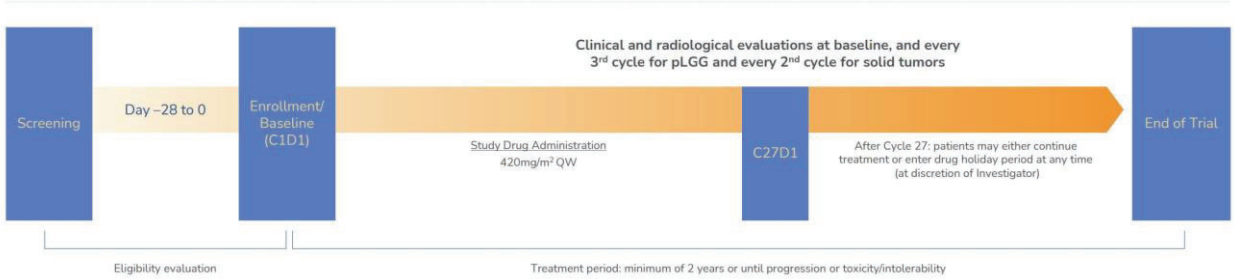


Figure 8. Design of the Phase 2 trial of tovorafenib (DAY101) in pLGG.

Tovorafenib (DAY101) is currently dosed as immediate-release tablets. We have developed a pediatric formulation suitable for oral dosing of children as young as six months of age and have dosed patients with this pediatric formulation in our pivotal Phase 2 FIREFLY-1 trial.

Comprehensive genomic profiling of newly-diagnosed or recurrent/progressive pLGG is standard practice within pediatric neuro-oncology programs across the United States, either utilizing CLIA/College of American Pathologists, or CAP, accredited hospital laboratories or third-party commercial vendors. In addition, the 2021 revision of the WHO Classification of Tumors of the Central Nervous System now includes assessment of BRAF mutation or fusion status as part of the diagnosis of LGGs. As a result, we expect that the vast majority of both newly diagnosed and relapsed pLGG patients with BRAF alterations will be identified. The technology platforms and solutions for the identification of the BRAF V600E mutation and BRAF wild-type fusions currently in use by individual investigators will be used to meet the clinical trial enrollment criteria, while we continue to work with regulatory authorities to ensure that any requirement for a companion diagnostic assay or device are met, for which we have entered into a collaboration with Foundation Medicine, Inc. to develop.

We have initiated a pivotal Phase 3 FIREFLY-2 trial of tovorafenib (DAY101) as a frontline therapy in pLGG. The first patient was dosed in March 2023. We believe that treating patients before they have undergone multiple rounds of toxic chemotherapy has the potential to both improve the efficacy of tovorafenib (DAY101) and reduce the overall burden of therapy and associated toxicities associated with the use of currently-employed cytotoxic agents.

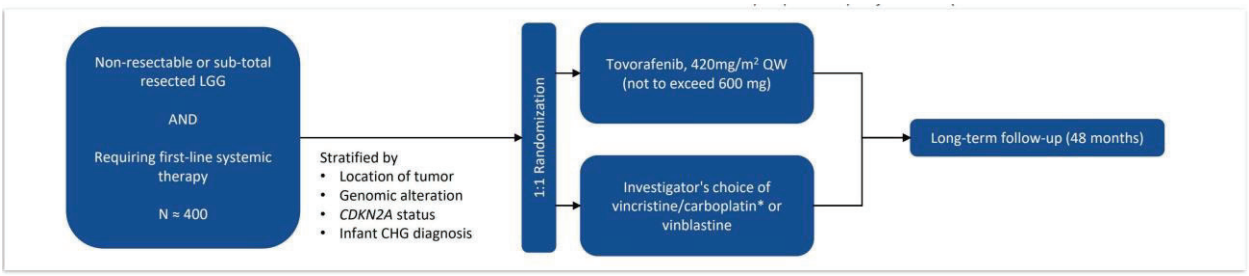


Figure 9. Design of the Phase 3 trial of tovorafenib (DAY101) in pLGG.

Potential market opportunity for tovorafenib (DAY101) in pLGG

Brain tumors are the most frequently occurring solid tumors in children. While pLGG is the most common brain tumor diagnosed, representing approximately 30% of all childhood brain tumors, the annual estimated incidence of pLGG is 1.3 to 2.1 per 100,000 in the United States, accounting for about 1,000–1,600 new diagnoses in 2015. Given the incidence of this disease, our team recognized the market opportunity for developing tovorafenib (DAY101) in this patient population based on the following rationale:

- Potential for tovorafenib (DAY101), a pan-RAF inhibitor, to be a high-impact targeted therapeutic in pLGG where approximately 70% of tumors are BRAF-altered pLGG in the United States.

- Premium reimbursement precedents for high impact therapeutics in rare diseases, oncology and pediatrics.
- Chronic duration of treatment required over many years to address these slow-growing and relentless tumors.
- High unmet medical need with limited current treatment alternatives for patients.
- Strong value proposition for physicians, patients and families.

We believe tovorafenib (DAY101), if approved, could become the standard of care for the treatment of pLGG. Due to the need for chronic administration, potentially over many years, the standard of care should be an effective, long-term therapeutic while providing a tolerability profile that minimizes long-term morbidity and treatment-associated toxicity. We believe that tovorafenib (DAY101) has the potential to provide long-term benefit—similar to effective therapies for more traditional chronic rare diseases—to patients with pLGG. Observations from the Phase 1 trial, tovorafenib's (DAY101) profile suggest that tovorafenib (DAY101) can potentially balance high rates of CNS penetrance leading to rapid and durable anti-tumor activity with favorable tolerability, a lack of serious adverse events in these pediatric patients, and clinical experience of long-term dosing of tovorafenib (DAY101) weekly for up to two years. We also believe that tovorafenib's (DAY101) oral, once-weekly dosing regimen would appeal to physicians, patients and their parents.

Potential applications of tovorafenib (DAY101) in other MAPK-driven tumors

To expand on our initial clinical development efforts in pediatric patients, we plan to explore tovorafenib (DAY101) in additional indications for adolescent and adult patient populations where various MAPK pathway alterations are believed to play an important role in driving disease. This is supported by data from over 225 adult patients dosed with tovorafenib (DAY101) in two separate Phase 1 trials previously conducted by Takeda. These trials also informed the starting dose level and weekly dosing regimen for future clinical trials, including the ongoing pivotal Phase 2 trial in pLGG. Results from these trials demonstrated that tovorafenib (DAY101) was well-tolerated in patients with advanced cancers, both alone and in combination with other anti-cancer agents, but because patients were not enriched for RAF alterations expected to respond to tovorafenib (DAY101) monotherapy, or studied in combinations that are now known to be more likely to lead to anti-tumor activity, only modest signs of efficacy were observed.

Based on data from preclinical studies, and building on the initial data from the Takeda-led Phase 1 trials, we have initiated an open-label, multicenter, Phase 1b/2a FIRELIGHT-1 umbrella master trial of tovorafenib monotherapy or combination therapy, which consists of two substudies. Substudy 1 is a Phase 2 clinical trial of tovorafenib (DAY101) as monotherapy in patients 12 years and older with RAF-altered tumors; the first patient was dosed in November 2021. Substudy 2 is a Phase 1b/2 combination trial of tovorafenib (DAY101) and pimasertib in patients 12 years and older with various MAPK-altered solid tumors; the first patient was dosed in May 2022. Simultaneous inhibition of both RAF and MEK has been shown to lead to synergistic antitumor activity in preclinical models. This combination may demonstrate enhanced anti-tumor activity in a variety of adult solid tumors driven by MAPK alterations, including NRAS mutant melanoma and lung cancers, tumors driven by Class II BRAF alterations, and tumors driven by KRAS alterations.

In the future, we may explore tovorafenib (DAY101) in combination with other selective inhibitors of key nodes in the MAPK signaling pathway. For example, a type II RAF inhibitor may provide synergistic benefit in combination with inhibitors of ERK or SHP2. We believe the ability of tovorafenib (DAY101) to inhibit multiple forms of RAF gene alterations, including wild-type RAF and RAF dimers, without triggering the liabilities of paradoxical activation observed with approved type I RAF inhibitors, enhance its profile as a potential backbone of combinations therapies designed to inhibit MAPK signaling in cancer.

Investigator-initiated trials of tovorafenib (DAY101)

We intend to leverage our relationships with academic investigators and pediatric oncology cooperative groups and consortia to explore the potential for tovorafenib (DAY101) in other rare pediatric tumor types.

A Phase 2 trial in relapsed Langerhans cell histiocytosis was initiated in March 2022 by the Children's Oncology Group, a National Cancer Institute-supported clinical trials group and the world's largest organization devoted exclusively to childhood and adolescent cancer research. This study is a single-arm non-randomized trial which has an estimated enrollment of 28 participants, who will be administered tovorafenib (DAY101) to determine overall response rate for children and young adults with relapsed or refractory Langerhans cell histiocytosis.

A second Phase 2 trial in craniopharyngioma was initiated in July 2022 by the Pacific Pediatric Neuro-Oncology Consortium. This study is a randomized multi-arm trial, which has an estimate enrollment of 56 patients, who will be administered nivolumb and tovorafenib (DAY101) in combination with nivolumb to assess the tolerability and efficacy of combination therapy with PD-1 (nivolumab) and pan-RAF-kinase (tovorafenib) inhibition for the treatment of children and young adults with craniopharyngioma.

Pimasertib

Pimasertib is an oral, highly-selective allosteric small molecular inhibitor of mitogen-activated protein kinase kinases 1 and 2 (MEK). Published preclinical studies indicated that pimasertib has higher CNS penetration than other MEK inhibitors. We obtained an exclusive license to pimasertib from Merck KGaA, Darmstadt, Germany in February 2021, and initiated a Phase 1b/2 umbrella master trial in MAPK-altered tumors in March 2022 to study the potentially beneficial combination of tovorafenib (DAY101) and pimasertib in patients 12 years and older. Merck KGaA, Darmstadt, Germany previously undertook extensive non-clinical and clinical development work through Phase 2, including a solid tumor trial in Japan and combinations of pimasertib with other agents. Pimasertib showed monotherapy clinical activity, including an improvement in the objective response rate and progression free survival, but not overall survival, in patients NRAS-mutant melanoma when compared to dacarbazine in a prospective randomized Phase 2 trial. The main adverse events observed during the clinical development of pimasertib were typical for other in-class allosteric MEK inhibitors, including GI-related adverse events, elevation of CPK, skin rash, and visual disturbances.

Preclinical studies

MEK is a critical signaling node that lies downstream of RAS in the MAPK pathway, and is a unique dual-specificity kinase that phosphorylates both serine/threonine and tyrosine residues. MEK consists of two isoforms, MEK1 and MEK2, which in turn phosphorylate ERK1 and ERK2. Activated ERK1/2 control a diverse range of cellular processes through their many substrates (>160) that are located in cellular membranes, the cytoplasm and nucleus. Many of these are transcription factors that are important in cellular proliferation, differentiation, survival, angiogenesis and migration.

As shown below in Figure 10, in cancers driven by elevated RAS or RAF signaling, inhibition of MEK releases the blockade on RAS and can contribute to increased RAS-mediated signaling and pathway activation, further desensitizing the cells to MEK inhibition. MEK inhibitors given as a monotherapy have demonstrated limited anti-tumor activity in preclinical tumor models of elevated RAS or RAF signaling. Most cancers that acquire resistance to MEKi and continue to proliferate do so through reactivation of the MAPK pathway and subsequent reactivation of ERK. ERK reactivation can occur through alterations or mutations to molecules upstream of ERK in the MAPK pathway such as RAS, RAF, NF1, or MEK. One approach to circumvent the overactivation of RAS signaling in such tumor models has been to combine a RAF inhibitor with a MEK inhibitor to inhibit the pathway at two different nodes which has been shown by multiple groups to result in synergistic effects on inhibiting cell and tumor model growth.

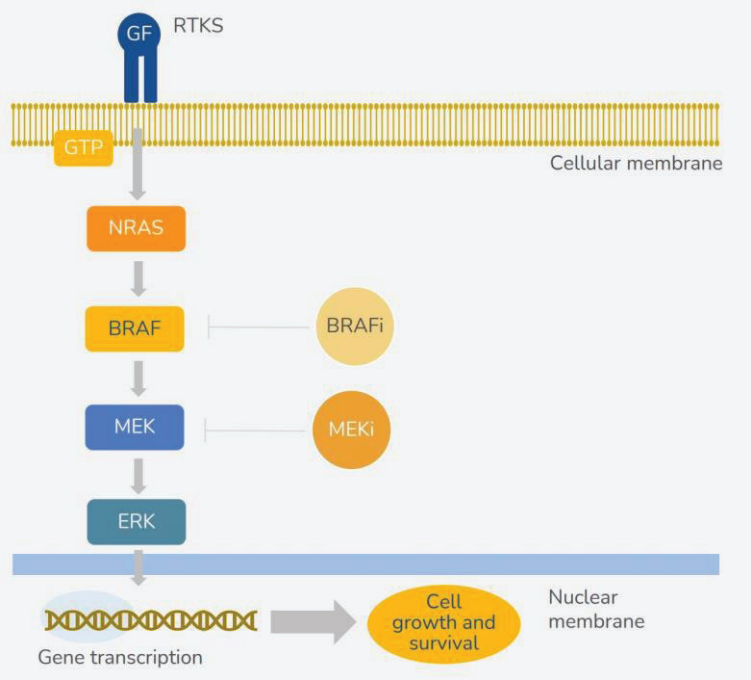


Figure 10: Dual inhibition of BRAF and MEK is an important strategy for addressing MAPK-driven tumors.

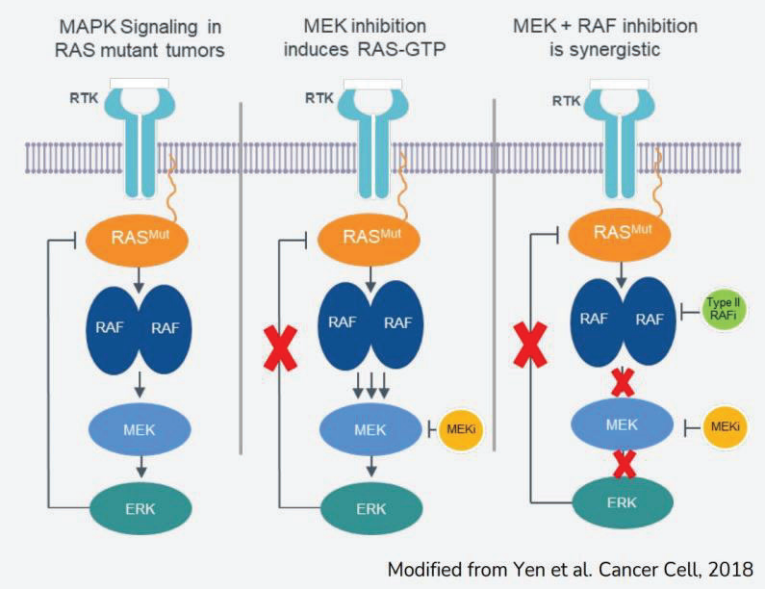


Figure 11. Model of the proposed mechanism of induced RAF inhibitor sensitivity. Left panel: under basal conditions, the MAPK pathway has multiple feedback loops negatively regulating upstream pathway activation, including RAS-GTP levels and RAF activation, thereby ensuring optimal pathway signaling. Middle panel: upon MEK inhibitor treatment, these feedback loops are disabled resulting in RAS-GTP induction, BRAF/CRAF dimerization, and RAF kinase activation. Right panel: Combination treatment with a MEK inhibitor and a type II RAF inhibitor is expected to exhibit synergistic effects. Modified from Yen et al. Cancer Cell, 2018.

Consistent with this approach, preclinical experiments showed the combination of a type II RAF inhibitor and pimasertib indeed led to synergistic cell killing activity. Calu-6 cells, a human lung adenocarcinoma cell line containing a KRAS G12C mutation, was found to be sensitive to cell killing by both BGB-283, a type II RAF inhibitor, and pimasertib. Treatment of Calu-6 cells with a combination of these inhibitors resulted in greater cell killing, as the EC50 for a 3 µM dose of BGB-283 was lowered by approximately 60-fold in the presence of pimasertib. These results suggest treatment with a MEK inhibitor in the presence of a RAF inhibitor result in an added cell killing benefit than observed with either inhibitor alone.

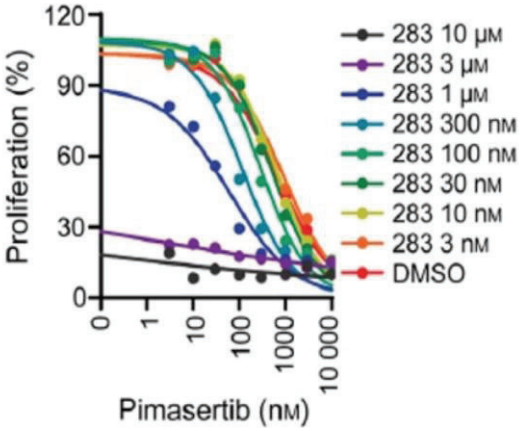


Figure 12. The sensitivity of Calu-6 cells to pimasertib was enhanced when cells were treated with BGB-283, a type II RAF inhibitor.

Similarly, in experiments with Calu-6 cells as well as NCI-H1792 cells, which contain a KRAS G12C mutation, cell lines were shown to be sensitive to either tovorafenib (DAY101) or MEKi-1 as monotherapy, however a combination of these inhibitors resulted in greater cell killing than observed with either inhibitor alone. These data further support the potential added benefit of combining a MEK inhibitor, with a type II RAF inhibitor, such as DAY 101 as a strategy to address certain MAPK-driven adult solid tumors.

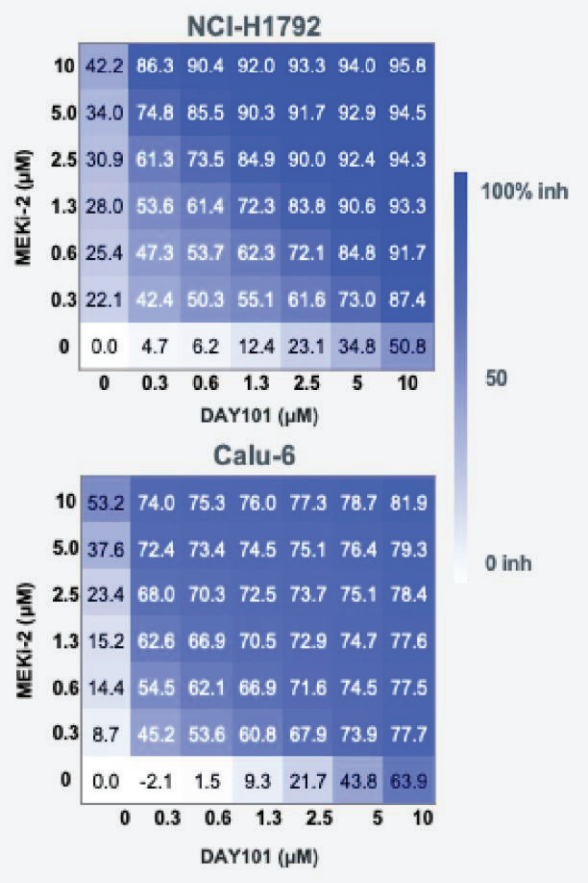


Figure 13. Synergy was observed with tovorafenib (DAY101) when combined with the MEK inhibitor in KRAS G12C or Q61 mutant tumor cell lines in vitro.

Clinical results

Pimasertib has been dosed in over 850 cancer patients in trials sponsored by Merck KGaA, Darmstadt, Germany KGaA, both as monotherapy and in combination with standard of care therapies, such as gemcitabine, dacarbazine, and the colorectal cancer regimen FOLFIRI, as well as selected investigational agents (the HDM2 inhibitor SAR405838, the PI3K/mTOR inhibitor SAR245409). To date, there have been no clinical trials investigating the potential of pimasertib in combination with a RAF inhibitor.

The initial Phase 1 trial of pimasertib was designed to evaluate different schedules and escalating doses of pimasertib monotherapy in patients with various solid tumors, including colorectal, melanoma, prostate, lung, and mesothelioma. The primary goal of this trial was to establish safety and pharmacokinetics to determine the most appropriate dose and schedule for further investigation. Preliminary efficacy was also assessed in terms of tumor response. While several examples of stable disease were observed across tumor types, multiple partial responses were observed in melanoma patients that triggered further investigations in this tumor type. In a dose expansion arm of this trial, 89 melanoma patients received pharmacologically active doses of pimasertib ranging from 28 mg to 255 mg/day across four dose regimens. The ORR was 12.4%, including one complete response, ten partial responses, and 46 patients with stable disease. In the Phase 1 monotherapy trial, dose limiting toxicities were mainly observed at doses of 120 mg/day or greater and included skin rash/acneiform dermatitis and ocular events, such as serous retinal detachment. The most common drug-related adverse events were consistent with effects observed with other MEK inhibitors, including diarrhea, skin disorders, ocular disorders, asthenia/fatigue, and peripheral edema. According to a publication of the results of the melanoma patients enrolled on the monotherapy Phase 1 clinical trial, TEAEs of Grade 3 or higher were experienced by eight out of the 69 patients enrolled. The TEAEs were skin events (n=4), ocular events (n=2) and diarrhea (n=2). All four skin events occurred in the continuous (R3) twice-daily group, whereas ocular and diarrhea events were reported in both the continuous twice-daily group and the

discontinuous group. High doses of pimasertib were associated with cases of retinal detachment; however, this and all other toxicities were manageable with supportive care and treatment interruption or dose reduction.

Merck KGaA, Darmstadt, Germany also conducted a multicenter, open-label, randomized Phase 2 trial in 194 patients with NRAS-mutated locally advanced or metastatic cutaneous melanoma, which compared single-agent pimasertib dosed at 60 mg BID to dacarbazine. Median progression free survival, or PFS, in pimasertib treated patients was 13.0 weeks, which was significantly longer than the 6.9 weeks observed in dacarbazine treated patients.

Clinical development plan

We have initiated an open-label, multicenter, Phase 1b/2a FIRELIGHT-1 umbrella master trial of tovorafenib monotherapy or combination therapy, which consists of two substudies. Substudy 1 is a Phase 2 clinical trial of tovorafenib (DAY101) as monotherapy in patients 12 years and older with RAF–altered tumors; the first patient was dosed in November 2021. Substudy 2 is a Phase 1b/2 combination trial of tovorafenib (DAY101) and pimasertib in patients 12 years and older with NRAS mutations, BRAFwt fusions and other BRAF mutations with the exception of V600E and V600K mutations; the first patient was dosed in May 2022. The combination substudy will be a Phase 1b dose ranging trial to establish the Phase 2 dose of tovorafenib (DAY101) in combination with pimasertib. Once this dose is established, patients will be enrolled in the combination dose expansion portion of this trial in cohorts defined by genetic aberration, such as NRAS mutation or BRAFwt fusion. The primary endpoint for the Phase 1b portion of the combination substudy is safety. For the monotherapy substudy in RAFwt fusions and RAF1 amplifications and the Phase 2 expansion cohorts, the primary endpoint is overall response rate and duration of response. Simultaneous inhibition of both RAF and MEK has been shown to lead to synergistic antitumor activity in preclinical models. This combination may demonstrate enhanced anti-tumor activity in a variety of adult solid tumors driven by MAPK alterations, including NRAS mutant melanoma and lung cancers, tumors driven by Class II BRAF alterations, tumors with BRAF wild-type fusions, and tumors driven by KRAS alterations.

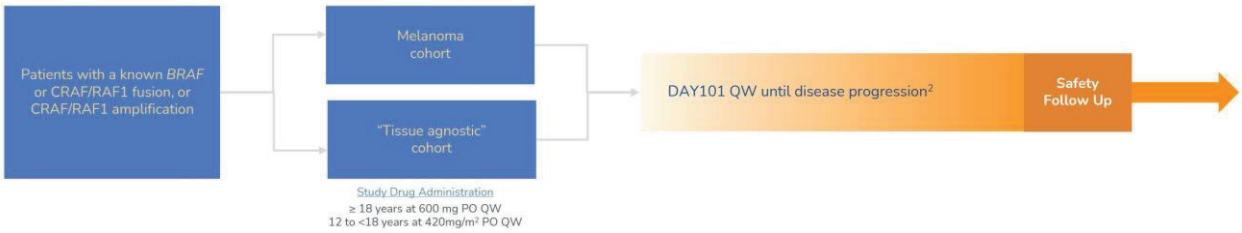


Figure 14. Umbrella master trial – DAY101-102 (main protocol) tovorafenib (DAY101) and MAPK pathway aberration, Substudy 1 monotherapy (DAY101-102a).

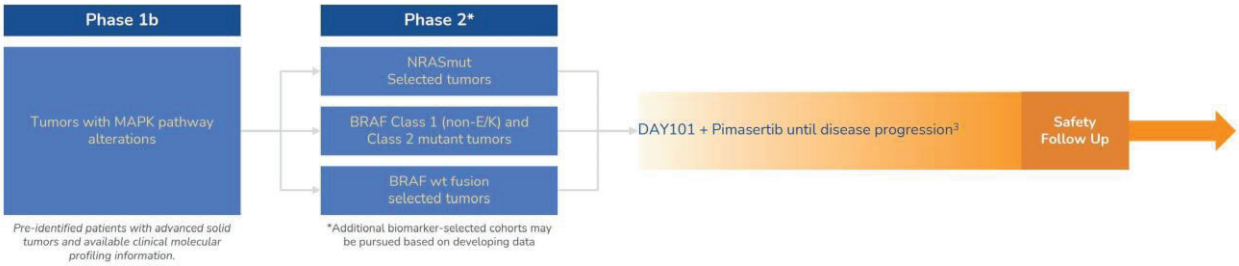


Figure 15. Umbrella master trial – DAY101-102 (main protocol) tovorafenib (DAY101) and MAPK pathway aberration, Substudy 2 MEK combo (DAY101-102b).

Preclinical data from multiple groups suggest that the combination of a MEK inhibitor, such as pimasertib, and a type II RAF inhibitor will have beneficial activity in various MAPK-driven tumor contexts, meaning that potent cell killing activity was obtained at lower concentrations of pimasertib than expected from data generated from monotherapy treatment. We believe that appropriate dosing of pimasertib in combination with tovorafenib (DAY101) may limit frequency and severity of adverse events observed with pimasertib alone, dosed at the MTD, owing to the ability to define a biologically active dose combination. We anticipate exploring pediatric combination trials once additional dosing and safety data is collected in adult patients.

Manufacturing

We do not own or operate, and currently have no plans to establish, any manufacturing facilities. We rely, and expect to continue to rely, on third parties for the manufacture of our product candidates for clinical testing, as well as for commercial manufacturing if any of our product candidates obtain marketing approval. We also rely, 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.

To date, we have contracted to obtain active pharmaceutical ingredients, or API, drug product, and packaging/distribution for our product candidates from STA Pharmaceutical Hong Kong Limited, Quotient Sciences – Philadelphia, LLC, Experic Services, and Fisher Clinical Services respectively, upon whom we currently rely as single-source contract manufacturing organizations, or CMOs. We have agreements under which third-party CMOs will generally provide us with necessary quantities of API, drug product, packaging/distribution on an order by order basis, based on our development needs. For commercial supply of tovorafenib, we are in the process of negotiating supply agreements to meet the anticipated commercial demand of the product. As we advance our product candidates through development, we will explore adding backup suppliers for the API, drug product, packaging and formulation for each of our product candidates to protect against any potential supply disruptions.

We generally expect to rely on third parties for the manufacture of any companion diagnostics we may develop.

Competition

The pharmaceutical and biotechnology industries are characterized by rapidly advancing technologies, intense competition and a strong emphasis on proprietary products. While we believe that our technology, the expertise of our team, and our development experience and scientific knowledge provide us with competitive advantages, we face increasing competition from many different sources, including pharmaceutical and biotechnology companies, academic institutions, governmental agencies and public and private research institutions. Product candidates that we successfully develop and commercialize may compete with existing therapies and new therapies that may become available in the future.

Many of our competitors, either alone or with their collaborators, have significantly greater financial resources, established presence in the market, and expertise in research and development, manufacturing, preclinical and clinical testing, obtaining regulatory approvals and reimbursement and marketing approved products than we do. These competitors also compete with us in recruiting and retaining qualified scientific and management personnel, establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs. Smaller or early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. Additional mergers and acquisitions may result in even more resources being concentrated in our competitors.

Our commercial potential could be reduced or eliminated if our competitors develop and commercialize products that are safer or more effective, have fewer or less severe side effects, and are more convenient or less expensive than products that we may develop. Our competitors also may obtain FDA or other regulatory approval for their products more rapidly than we can, which could result in our competitors establishing a strong market position before we are able to enter the market or could otherwise make our development more complicated. We believe the key competitive factors affecting the success of all of our programs are likely to be efficacy, safety and patient convenience.

We believe that tovorafenib (DAY101) has the potential to be the first pan-RAF inhibitor to be approved by the FDA, for use in the treatment of pLGG, as we are not aware of competing product candidates that are further along in the development process. However, this does not indicate that tovorafenib (DAY101) has been proven effective or that it will receive regulatory approval.

Three BRAF inhibitors have been approved by the FDA for the treatment of tumors containing V600E or V600K mutations. These first-generation BRAF inhibitors, known more generally as type I RAF inhibitors, are vemurafenib, marketed as Zelboraf® by Genentech; dabrafenib, marketed as Tafinlar® by Novartis; and encorafenib, marketed as Braftovi® by Pfizer. Dabrafinib, in combination with trametinib, marketed as Mekinist® by Novartis, has been approved for the treatment of adult and pediatric patients ≥ 6 years of age with unresectable or metastatic solid tumors with BRAF V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options. This includes BRAF V600E pLGG, a subset (approximately 10%-20%) of the greater RAF-altered pLGG clinical scope of the tovorafenib (DAY101) development program.

Four MEK inhibitors have been approved by the FDA. Three have been approved for the treatment of tumors containing BRAF V600E or V600K mutations, including cobimetinib, marketed as Cotellic® by Genentech; trametinib, marketed as Mekinist® by Novartis; and binimetinib, marketed as Mektovi® by Pfizer. A fourth MEK inhibitor–selumetinib, marketed as Koselugo® by AstraZeneca, has been approved for the treatment of pediatric patients, 2 years of age and older, with neurofibromatosis type 1, or NF1, who have symptomatic, inoperable plexiform neurofibromas.

Erasca is developing the next-generation BRAF inhibitor naporafenib (LXH254) in combination with various agents, in planned Phase 1 and Phase 3 clinical trials. BeiGene has two next-generation BRAF programs: lifirafenib (BGB-283), which is currently in a Phase 1/2 trial in combination with mirdametinib, and BGB-3245 which is currently in a single agent in Phase 1 dose escalation study. Hanmi and Genentech are developing belvarafenib in combination with cobimetinib in a Phase 1b clinical trial. Fore Therapeutics (formelly NovellusDx) is developing the RAF dimer breaker PLX8394 in a Phase 1/2 trial in combination with cobicistat. Kinnate is developing KIN-2787 in monotherapy phase 1 clinical trial. Black Diamond Therapeutics have next-generation BRAF inhibitors in various stages of preclinical development.

With regard to the treatment of pLGG, dabrafenib, in combination with trametinib, is being evaluated in a Novartis-sponsored randomized Phase 2 clinical trial in newly diagnosed patients with BRAF V600 mutant pLGG. Novartis has announced their plans to file a Supplemental New Drug Application based on data of this trial in early 2023. Further, some MEK inhibitors and some type I RAF inhibitors and other targeted therapies are being studied in academic investigator-initiated clinical trials, and in some regions may be being used in an off-label manner. These agents may represent competition for tovorafenib (DAY101) when it enters the market.

Significant Agreements

Takeda asset agreement and Millennium stock exchange agreement

On December 16, 2019, DOT Therapeutics-1, Inc., or DOT-1, our subsidiary, entered into an asset purchase agreement, or the Takeda Asset Agreement, with Millennium Pharmaceuticals, Inc., a related party and an affiliate of Takeda Pharmaceutical Company Limited, or Takeda. Pursuant to the Takeda Asset Agreement, DOT-1 purchased certain technology rights and know-how related to TAK-580 (which is now tovorafenib (DAY101)) that provides a new approach for treating patients with primary brain tumors or brain metastases of solid tumors. DOT-1 also received clinical inventory supplies to use in our research and development activities of such RAF-inhibitor and an assigned investigator clinical trial agreement. Takeda also assigned to DOT-1 its exclusive license agreement, or the Viracta License Agreement, with Viracta Therapeutics, Inc. (f/k/a Sunesis Pharmaceuticals, Inc.), or Viracta. Takeda also granted DOT-1 a worldwide, sublicensable exclusive license under specified patents and know-how and non-exclusive license under other patents and know-how generated by Takeda under the Takeda Asset Agreement. DOT-1 also granted Takeda a grant back license, as defined in the Takeda Asset Agreement, which is terminable either automatically or by DOT-1 in the event Takeda does not achieve specified development milestones within the applicable timeframes set forth under the Takeda Asset Agreement. This grant back license to Takeda was terminated at the time of Conversion in connection with the Millennium Stock Exchange Agreement.

In consideration for the sale and assignment of assets and the grant of the license under the Takeda Asset Agreement, DOT-1 made an upfront payment of $1.0 million in cash and issued 9,857,143 shares of Series A redeemable convertible preferred stock in DOT-1 in December 2019. The fair value of issued shares was estimated as $9.9 million, based on the price paid by other investors for issued shares in the Series A financing of DOT-1. Based on the terms of the Millennium Stock Exchange Agreement, Takeda exchanged the 9,857,143 shares of Series A redeemable convertible preferred stock of DOT-1 for 6,470,382 shares of our common stock upon the effectiveness of the Conversion, on May 26, 2021.

The term of the Takeda Asset Agreement will expire on a country-by-country basis upon expiration of all assigned patent rights and all licensed patent rights in such country. Takeda may terminate the Takeda Asset Agreement prior to our first commercial sale of a product if we cease conducting any development activities for a continuous and specified period of time and such cessation is not agreed upon by the parties and is not done in response to guidance from a regulatory authority. Additionally, Takeda can terminate the Takeda Asset Agreement in the event of our bankruptcy. In the event of termination of the Takeda Asset Agreement by Takeda as a result of our cessation of development or bankruptcy, all assigned patents, know-how and contracts (other than the Viracta License Agreement) will be assigned back to Takeda and Takeda will obtain a reversion license under patents and know-how generated to exploit all such terminated products.

Effective December 31, 2021, DOT-1 was merged with and into our company, with our company being the surviving corporation and assuming DOT-1's obligations under the Takeda Assets Purchase Agreement.

Viracta license agreement

On December 16, 2019, DOT-1 amended and restated the Viracta License Agreement that was assigned pursuant to the Takeda Asset Agreement. Under the Viracta License Agreement, DOT-1 received a worldwide exclusive license under specified patent rights and know-how to develop, use, manufacture, and commercialize products containing compounds binding the RAF protein family.

DOT-1 paid $2.0 million upfront in cash to Viracta, which was recorded as research and development expenses in 2019. DOT-1 made a milestone payment of $3.0 million to Viracta in February 2021, which was recorded as research and development expense when the milestone was achieved in April 2021. DOT-1 is also required to make additional milestone payments of up to $54.0 million upon achievement of specified development and regulatory milestones for each licensed product in two indications, with milestones payable for the second indication to achieve a specified milestone event being lower than milestones payable for the first indication. Additionally, if DOT-1 obtains a priority review voucher with respect to a licensed product and sells such priority review voucher to a third party or uses such priority review voucher, DOT-1 is obligated to pay Viracta a specified percentage in the mid-teen digits of all net consideration received from any such sale or of the value of such used priority review voucher, as applicable. Commencing on the first commercial sale of a licensed product in a country, DOT-1 is obligated to pay tiered royalties ranging in the mid-single-digit percentages on net sales of licensed products, if any. The obligation to pay royalties will end on a country-by-country and licensed product-by-licensed product basis commencing on the first commercial sale in a country and continuing until the later of: (i) the expiration of the last valid claim of the Viracta licensed patents, jointly owned collaboration patents or specified patents owned by us covering the use or sale of such product in such country, (ii) the expiration of the last statutory exclusivity pertaining to such product in such country or (iii) the tenth anniversary of the first commercial sale of such product in such country. No other milestones, except as discussed above, were achieved and due as of December 31, 2022.

The term of the Viracta License Agreement will expire on a licensed product-by-licensed product and country-by-country basis upon the expiration of our obligation to pay royalties to Viracta with respect to such product in such country. DOT-1 has the right to terminate the Viracta License Agreement with respect to any or all of the licensed products at will upon a specified notice period.

Effective December 31, 2021, DOT-1 was merged with and into our company, with our company being the surviving corporation and assuming DOT-1's obligations under Viracta License Agreement.

License agreement with Merck KGaA, Darmstadt, Germany

On February 10, 2021, DOT Therapeutics-2, Inc., or DOT-2, our subsidiary, entered into a license agreement, or the MRKDG License Agreement, with Merck KGaA, Darmstadt, Germany, a pharmaceutical corporation located in Darmstadt, Germany. Under the MRKDG License Agreement, Merck KGaA, Darmstadt, Germany granted to us an exclusive worldwide license, with the right to grant sublicenses through multiple tiers, under specified patent rights and know-how for us to research, develop, manufacture and commercialize products containing and comprising the pimasertib and MSC2015103B compounds. We also received clinical inventory supplies to use in our research and development activities. Our exclusive license grant is subject to a non-exclusive license granted by Merck KGaA, Darmstadt, Germany's affiliate to a cancer research organization and Merck KGaA, Darmstadt, Germany retains the right to conduct, directly or indirectly, certain ongoing clinical studies relating to pimasertib.

Under the MRKDG License Agreement, we have obligations to use commercially reasonable efforts to develop and commercialize at least two licensed products in at least two specified major market countries by the year 2029.

In consideration for the rights granted under the MRKDG License Agreement and clinical supplies, we made an upfront payment of $8.0 million, which was recorded as research and development expenses, as the technology does not have an alternative future use and supplies are used for research activities. Additionally, we made a milestone payment of $2.5 million, which was recorded as research and development expenses due to the nature of the license agreement and the milestone event relating to the first dosing of a patient in a first clinical trial of a product containing pimasertib, in the year ended December 31, 2022. We may also be required to make additional payments of up to $364.5 million based upon the achievement of specified development, regulatory, and commercial milestones, as well a high, single-digit royalty percentage on future net sales of licensed products, if any. Milestones and royalties are contingent upon future events and will be recorded when the milestones are achieved and when payments are due.

The term of the MRKDG License Agreement will expire on a licensed product-by-licensed product and country-by-country basis upon the expiration of our obligation to pay royalties to the licensor with respect to such licensed product in such country and will expire in its entirety upon the expiration of all of our payment obligations with respect to all licensed products and all countries under the MRKDG License Agreement.

Effective December 31, 2021, DOT-2 was merged with and into our company, with our company being the surviving corporation and assuming DOT-2's obligations under the MRKDG License Agreement.

Intellectual Property

Our commercial success depends in part on our ability to obtain and maintain proprietary or intellectual property protection for our drug candidates, technology and know-how, to operate without infringing the proprietary or intellectual property rights of others and to prevent others from infringing our proprietary or intellectual property rights. We expect that we will seek to protect our proprietary and intellectual property position by, among other methods, pursuing and obtaining patent protection in the United States and in jurisdictions outside of the United States related to our proprietary technology, inventions, improvements and drug candidates that are important to the development and implementation of our business. We also rely on trade secrets, know-how, trademarks, continuing technological innovation and licensing opportunities to develop and maintain our proprietary and intellectual property position. Presently, our patent portfolio includes issued patents and pending patent applications that are in-licensed, owned and/or co-owned by us.

We currently, and expect that we will continue to, own, co-own or in-license patent applications and issued patents related to our drug candidates, as well as their use in the treatment of various diseases such as pediatric cancers. For our drug candidates, we generally pursue multilayered patent protection covering compositions of matter, methods of use and methods of manufacture. We intend to strengthen the patent protection of our drug candidates and technologies through additional patent application filings.

As of January 1, 2023, we owned or co-owned a patent portfolio consisting of ten patent families, exclusively in-license three patent families from Merck KGaA, Darmstadt, Germany, and non-exclusively in-license one patent family from Takeda Pharmaceutical Company Limited. The ten patent families that we own or co-own include patent applications and issued patents that cover compositions of matter, pharmaceutical compositions, methods of synthesis, synthetic intermediates, methods of treatment and combination therapies related to one of our product candidates: tovorafenib (DAY101) or pimasertib. The non-exclusively in-licensed patent family from Takeda Pharmaceutical Company Limited covers a catalyst that may be used in a preparation of our product candidate tovorafenib (DAY101). The three exclusively in-licensed patent families from Merck KGaA, Darmstadt, Germany cover compositions of matter and methods of use for our product candidate pimasertib. Patent terms for our owned, co-owned or licensed patents discussed herein exclude any patent term extension that may be available.

Our owned or co-owned patent portfolio, as of January 1, 2023, includes a co-owned patent family that is directed to the compositions of matter and methods of use of tovorafenib (DAY101) with four issued U.S. patents and multiple foreign patents and applications including granted patents in Germany, France, United Kingdom, Belgium, Switzerland, Denmark, Spain, Ireland, Italy, Netherlands, Australia, Brazil, Canada, China, India, Japan, Korea, Mexico, Singapore, South Africa, Taiwan, and Hong Kong, which are expected to expire between 2028 and 2031.

Our owned or co-owned patent portfolio includes a patent family that is directed to pharmaceutical formulations of tovorafenib (DAY101) with an issued U.S. patent and multiple foreign patents and applications including granted patents in Germany, France, United Kingdom, Belgium, Brazil, Canada, Switzerland, Spain, Ireland, Italy, Luxembourg, Monaco, Japan, and China, which are expected to expire in 2035. Our owned or co-owned patent portfolio includes an additional pharmaceutical formulation patent family that is directed to formulations of tovorafenib (DAY101) including pending applications in the United States, Europe, China and Japan that, if issued, are expected to expire in 2040. Our owned or co-owned patent portfolio includes a patent family with one U.S. provisional application directed to additional formulations of tovorafenib (DAY101) that, if converted to a non-provisional application and issued, is expected to expire in 2043. Our owned or co-owned patent portfolio also includes a patent family directed to methods of synthesizing tovorafenib (DAY101) including an issued U.S. patent, and granted patents in Australia, Eurasia, Israel, Japan, and Mexico which are expected to expire in 2038 as well as pending applications in the United States and Europe that, if issued, are expected to expire in 2038. Our owned or co-owned patent portfolio further includes a patent family directed to methods of treating cancer using tovorafenib (DAY101) in combination with docetaxel with multiple foreign patents including granted patents in China, Germany, France, United Kingdom, Belgium, Switzerland, Spain, Ireland, Italy, Luxembourg, and Monaco that are expected to expire in 2035. Our owned or co-owned patent portfolio includes a patent family with a pending PCT application directed to methods of treating pLGG that, if nationalized and issued, is expected to expire in 2041. Our owned or co-owned patent portfolio includes a patent family with a pending PCT application directed to methods of treating cancer using tovorafenib (DAY101) in combination with a MEK inhibitor such as pimasertib that, if nationalized and issued, is expected to expire in 2042. Our owned or co-owned patent portfolio includes a patent family with a pending PCT application directed to methods of selecting patients for treatment with tovorafenib (DAY101) that, if nationalized and issued, is expected to expire in 2042. Our owned or co-owned patent portfolio further includes a patent family with one U.S. provisional application directed to methods of treatment with a MEK inhibitor such as pimasertib that, if converted to a non-provisional application and issued, is expected to expire in 2043.

Our patent portfolio, as of January 1, 2023, includes a patent family exclusively in-licensed from Merck KGaA, Darmstadt, Germany that covers the composition of matter and methods of use of pimasertib. This patent family includes four issued U.S. patents and multiple foreign patents and/or applications including granted patents in Argentina, Austria, Australia, Belgium, Bulgaria, Brazil, Canada, Switzerland, China, Cyprus, Czech Republic, Germany, Denmark, Eurasia, Estonia, Spain, Finland, France, United Kingdom, Greece, Hong Kong, Hungary, Ireland, Israel, India, Iceland, Italy, Japan, Korea, Lithuania, Luxembourg, Latvia, Monaco, Mexico, Netherlands, Norway, Poland, Portugal, Romania, Russian Federation, Sweden, Singapore, Slovenia, Slovakia, Turkey, Ukraine, and South Africa that are expected to expire between 2025 and 2028. Our patent portfolio includes a patent family exclusively in-licensed from Merck KGaA, Darmstadt, Germany that is directed to the solid state form of pimasertib. This patent family includes one issued U.S. patent and multiple foreign patents and/or applications, including granted patents in Austria, Australia, Belgium, Canada, Switzerland, Czech Republic, Germany, Denmark, Eurasia, Spain, France, United Kingdom, Italy, Japan, Luxembourg, Mexico, Netherlands, Poland, Portugal, Russian Federation, Sweden, Singapore, Taiwan, and South Africa, which are expected to expire in 2033. Our patent portfolio further includes a patent family exclusively in-licensed from Merck KGaA, Darmstadt, Germany that covers the composition of matter and methods of use of MSC2015103B with two issued U.S. patents and multiple foreign patents and/or applications, including granted patents in Argentina, Austria, Australia, Belgium, Brazil, Canada, Switzerland, China, Czech Republic, Germany, Denmark, Eurasia, Estonia, Spain, Finland, France, United Kingdom, Hong Kong, Croatia, Hungary, Ireland, Israel, India, Iceland, Italy, Korea, Lithuania, Luxembourg, Latvia, North Macedonia, Malta, Mexico, Netherlands, Norway, New Zealand, Philippines, Poland, Portugal, Romania, Russian Federation, Sweden, Singapore, Slovenia, Slovakia, Turkey, Ukraine, and South Africa, which are expected to expire in 2029.

The term of individual patents depends upon the legal term for patents in the countries in which they are granted. In most countries in which we file, the patent term is generally 20 years from the earliest date of filing a non-provisional patent application. In the United States, the patent term may, in certain cases, be lengthened by patent term adjustment, which compensates a patentee for administrative delays by the U.S. Patent and Trademark Office, or USPTO, in examining and granting a patent or may be shortened if a patent is terminally disclaimed over a commonly owned patent or a patent naming a common inventor and having an earlier expiration date. Additionally, the Drug Price Competition and Patent Term Restoration Act of 1984, or the Hatch-Waxman Act, permits patent term extension of up to five years beyond the expiration date of a U.S. patent as partial compensation for the length of time a drug is under regulatory review while a patent that covers the drug is in force. The length of the patent term extension is related to the length of time the drug is under regulatory review. Patent term extension cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval, only one patent applicable to each regulatory review period may be extended and only those claims covering the approved drug, a method for using it or a method for manufacturing it may be extended.

Similar provisions are available in the European Union and certain other foreign jurisdictions to extend the term of a patent that covers an approved drug. In the future, if and when our drug candidates receive approval by the FDA or foreign regulatory authorities, we expect to apply for patent term extensions on issued patents covering those products, if available. However, there is no guarantee that the applicable authorities, including the FDA in the United States, will agree with our assessment of whether such extensions should be granted, and, if granted, the length of such extensions. For more information regarding the risks related to our intellectual property, see the section titled "Risk Factors–Risks Related to Our Intellectual Property." Expiration dates referred to above are without regard to potential patent term extension or other market exclusivity that may be available to us.

The patent positions of biopharmaceutical companies like ours are generally uncertain and involve complex legal, scientific and factual questions. Our commercial success will also depend in part on not infringing upon the proprietary rights of third parties. It is uncertain whether the issuance of any third-party patent would require us to alter our development or commercial strategies, alter our drugs or processes, obtain licenses or cease certain activities. Our breach of any license agreements or our failure to obtain a license to proprietary rights required to develop or commercialize our future products may have a material adverse impact on us. If third parties prepare and file patent applications in the United States that also claim technology to which we have rights, we may have to participate in interference or derivation proceedings in the USPTO to determine priority of invention. For more information, see the section titled "Risk Factors–Risks Related to Our Intellectual Property."

In addition to patent protection, we also rely on trade secrets, know-how, trademarks, other proprietary information and continuing technological innovation to develop and maintain our competitive position. Our trademark portfolio currently contains registration applications and/or registrations for Day One, Day One Biopharmaceuticals, and Cancer Drug Development Comes of Age in the United States. We seek to protect and maintain the confidentiality of proprietary information to protect aspects of our business that are not amenable to, or that we do not consider appropriate for, patent protection. Although we take steps to protect our proprietary information and trade secrets, including through contractual means with our employees and consultants, third parties may independently develop substantially equivalent proprietary information and techniques or otherwise gain access to our trade secrets or disclose our technology. Thus, we may not be able to meaningfully protect our trade secrets. It is our policy to require our employees, consultants, outside scientific collaborators, sponsored researchers and other advisors to execute confidentiality agreements upon the commencement of employment or consulting relationships with us. These agreements provide that all confidential information concerning our business or financial affairs developed or made known to the individual during the course of the individual's relationship with us is to be kept confidential and not disclosed to third parties except in specific circumstances. Our agreements with employees also provide that all inventions conceived by the employee in the course of employment with us or from the employee's use of our confidential information are our exclusive property. However, such confidentiality agreements and invention assignment agreements can be breached, and we may not have adequate remedies for any such breach. For more information regarding the risks related to our intellectual property, see "Risk Factors—Risks Related to Our Intellectual Property."

Government Regulation

Government authorities in the United States, at the federal, state and local level, and in other countries and jurisdictions extensively regulate, among other things, the research, development, testing, manufacture, quality control, approval, packaging, storage, recordkeeping, labeling, advertising, promotion, distribution, marketing, post-approval monitoring and reporting, and import and export of pharmaceutical products. The processes for obtaining regulatory approvals in the United States and in foreign countries and jurisdictions, along with subsequent compliance with applicable statutes and regulations and other regulatory authorities, require the expenditure of substantial time and financial resources.

FDA approval process

In the United States, pharmaceutical products are subject to extensive regulation by the FDA, pursuant to the Federal Food, Drug, and Cosmetic Act, and other federal and state statutes and regulations that govern, among other things, the research, development, testing, manufacture, storage, recordkeeping, approval, labeling, promotion and marketing, distribution, post-approval monitoring and reporting, sampling and import and export of pharmaceutical products. Failure to comply with applicable U.S. requirements may subject a company to a variety of administrative or judicial sanctions, such as clinical hold, FDA refusal to approve pending NDAs, warning or untitled letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, civil penalties and criminal prosecution.

Pharmaceutical product development for a new product or certain changes to an approved product in the United States typically involves preclinical laboratory and animal tests, the submission to the FDA of an IND, which must become effective before clinical testing may commence, and adequate and well-controlled clinical trials to establish the safety and effectiveness of the drug for each indication for which the FDA approval is sought. Satisfaction of FDA pre-market approval requirements typically takes many years and the actual time required may vary substantially based upon the type, complexity and novelty of the product or disease.

Preclinical tests include laboratory evaluation of product chemistry, formulation and toxicity, as well as animal trials to assess the characteristics and potential safety and efficacy of the product. The conduct of the preclinical tests must comply with federal regulations and requirements, including good laboratory practices. The results of preclinical testing are submitted to the FDA as part of an IND along with other information, including information about product chemistry, manufacturing and controls, and a proposed clinical trial protocol. Long-term preclinical tests, such as animal tests of reproductive toxicity and carcinogenicity, may continue after the IND is submitted. A 30-day waiting period after the submission of each IND is required prior to the commencement of clinical testing in humans. If the FDA has neither commented on nor questioned the IND within this 30-day period, the clinical trial proposed in the IND may begin. Clinical trials involve the administration of the investigational new drug to healthy volunteers or patients under the supervision of a qualified investigator. Clinical trials must be conducted: (i) in compliance with federal regulations; (ii) in compliance with Good Clinical Practice, or GCP, an international standard 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 the objectives of the trial, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated. Each protocol involving testing on U.S. patients and subsequent protocol amendments must be submitted to the FDA as part of the IND.

The FDA may order the temporary, or permanent, discontinuation of a clinical trial at any time, or impose other sanctions, if it believes that the clinical trial either is not being conducted in accordance with FDA requirements or presents an unacceptable risk to the clinical trial patients. Imposition of a clinical hold may be full or partial. The study protocol and informed consent information for patients in clinical trials must also be submitted to an institutional review board, or IRB, for approval. The IRB will also monitor the clinical trial until completed. An IRB may also require the clinical trial at the site to be halted, either temporarily or permanently, for failure to comply with the IRB's requirements, or may impose other conditions. 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.

Clinical trials to support NDAs for marketing approval are typically conducted in three sequential phases, but the phases may overlap. In Phase 1, the initial introduction of the drug into healthy human subjects or patients, the drug is tested to assess metabolism, pharmacokinetics, pharmacological actions, side effects associated with increasing doses, and, if possible, early evidence of effectiveness. Phase 2 usually involves trials in a limited patient population to determine the effectiveness of the drug for a particular indication, dosage tolerance and optimum dosage, and to identify common adverse effects and safety risks. If a drug demonstrates evidence of effectiveness and an acceptable safety profile in Phase 2 evaluations, Phase 3 trials are undertaken to obtain the additional information about clinical efficacy and safety in a larger number of patients, typically at geographically dispersed clinical trial sites, to permit the FDA to evaluate the overall benefit-risk relationship of the drug and to provide adequate information for the labeling of the drug. In most cases, the FDA requires two adequate and well-controlled Phase 3 clinical trials to demonstrate the efficacy of the drug. A single trial may be sufficient in rare instances, including (1) where the study is a large multicenter trial demonstrating internal consistency and a statistically very persuasive finding of a clinically meaningful effect on mortality, irreversible morbidity or prevention of a disease with a potentially serious outcome and confirmation of the result in a second trial would be practically or ethically impossible or (2) when in conjunction with other confirmatory evidence.

These Phases may overlap or be combined. For example, a Phase 1/2 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 subjects 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.

The manufacturer of an investigational drug in a Phase 2 or 3 clinical trial for a serious or life-threatening disease is required to make available, such as by posting on its website, its policy on evaluating and responding to requests for expanded access.

After completion of the required clinical testing, an NDA is prepared and submitted to the FDA. The FDA approval of the NDA is required before marketing of the product may begin in the United States. The NDA must include the results of all preclinical, clinical and other testing and a compilation of data relating to the product's pharmacology, chemistry, manufacture and controls.

The cost of preparing and submitting an NDA is substantial. The submission of most NDAs is additionally subject to a substantial application user fee. 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 NDAs for products designated as orphan drugs, unless the product also includes a non-orphan indication. The applicant under an approved NDA is also subject to annual program fees. The FDA adjusts the user fees on an annual basis, and the fees typically increase annually.

The FDA reviews each submitted NDA before it determines whether to file it, based on the agency's threshold determination that it is sufficiently complete to permit substantive review, and the FDA may request additional information. The FDA must make a decision on whether to file an NDA within 60 days of receipt, and such decision could include a refusal to file by the FDA. If the submission is filed, the FDA begins an in-depth review of the NDA. The FDA has agreed to certain performance goals in the review of NDAs. Most applications for standard review drug products are reviewed within 10 to 12 months; most applications for priority review drugs are reviewed in six to eight months. Priority review can be applied to drugs that the FDA determines offer major advances in treatment or provide a treatment where no adequate therapy exists. 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 goal dates for standard and priority NDAs, and the review process can be extended by FDA requests for additional information or clarification.

The FDA may also refer applications for novel drug products, or drug products that present difficult questions of safety or efficacy, to an outside 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 the recommendation of an advisory committee, but it generally follows such recommendations.

Before approving an NDA, the FDA will conduct a pre-approval inspection of the manufacturing facilities for the new product 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 typically inspects one or more clinical trial sites to ensure compliance with GCP requirements and the integrity of the data supporting safety and efficacy.

After the FDA evaluates the NDA and the manufacturing facilities, it issues either an approval letter or a complete response letter, or CRL. A CRL generally outlines the deficiencies in the submission and may require substantial additional testing, or information, in order for the FDA to reconsider the application, such as additional clinical data, additional pivotal clinical trial(s), and/or other significant and time-consuming requirements related to clinical trials, preclinical studies or manufacturing. If a CRL is issued, the applicant may resubmit the NDA addressing all of the deficiencies identified in the letter, withdraw the application, engage in formal dispute resolution or request an opportunity for a hearing. The FDA has committed to reviewing 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 NDA does not satisfy the criteria for approval.

If, or when, the deficiencies identified in the CRL have been addressed to the FDA's satisfaction in a resubmission of the NDA, the FDA will issue an approval letter. An approval letter authorizes commercial marketing of the drug with specific prescribing information for specific indications. As a condition of NDA approval, the FDA may require a risk evaluation and mitigation strategy, or REMS, to help ensure that the benefits of the drug outweigh the potential risks to patients. A REMS can include medication guides, communication plans for healthcare professionals, and elements to assure safe use, or ETASU. ETASU can include, but are not limited to, special training or certification for prescribing or dispensing, dispensing only under certain circumstances, special monitoring, and the use of patient registries. The requirement for a REMS can materially affect the potential market and profitability of the drug. Moreover, product approval may require substantial post-approval testing and surveillance to monitor the drug's safety or efficacy. Once granted, product approvals may be withdrawn if compliance with regulatory standards is not maintained or problems are identified following initial marketing.

Changes to some of the conditions established in an approved application, including changes in indications, labeling, or manufacturing processes or facilities, require submission and FDA approval of an NDA supplement or, in some cases, a new NDA, before the change can be implemented. An NDA supplement for a new indication typically requires clinical data similar to that in the original application, and the FDA uses the same procedures and actions in reviewing NDA supplements as it does in reviewing NDAs.

Disclosure of clinical trial information

Sponsors of clinical trials of FDA-regulated products, including drugs, are required to register and disclose certain clinical trial information. Information related to the product, patient population, phase of investigation, study sites and investigators, and other aspects of the clinical trial, is then made public as part of the registration. Sponsors are also obligated to discuss the results of their clinical trials after completion. Disclosure of the results of these trials can be delayed in certain circumstances for up to two years after the date of completion of the trial. Competitors may use this publicly available information to gain knowledge regarding the progress of development programs.

Orphan drugs

Under the Orphan Drug Act, the FDA may grant orphan drug designation to drugs 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 more than 200,000 individuals in the United States but 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 an NDA. After the FDA grants orphan drug designation, the identity of the drug and its potential orphan use are disclosed publicly by the FDA. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process.

The first NDA applicant to receive FDA approval for a particular active moiety to treat a rare disease for which it has such designation is entitled to a seven-year exclusive marketing period in the United States for that product, for that indication. During the seven-year exclusivity period, the FDA may not approve any other applications to market the same drug for the same disease, except in limited circumstances, such as a showing of clinical superiority to the product with orphan drug 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 drug for the same disease or condition, or the same drug for a different disease or condition. Other benefits of orphan drug designation include tax credits for certain research and an exemption from the NDA user fee.

Breakthrough therapy designation

The FDA is also required to expedite the development and review of applications for approval of drugs that are intended to treat a serious or life-threatening disease or condition where preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints. Under the breakthrough therapy program, the sponsor of a new product candidate may request that the FDA designate the product candidate for a specific indication as a breakthrough therapy concurrent with, or after, the filing of the IND for the product candidate. The FDA must determine if the product candidate qualifies for breakthrough therapy designation within 60 days of receipt of the sponsor's request. The FDA may take certain actions with respect to breakthrough therapies, including holding meetings with the sponsor throughout the development process, providing timely advice to the product 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.

Accelerated approval

Accelerated approval may be granted for a product that is intended to treat a serious or life-threatening condition and that generally provides a meaningful therapeutic advantage to patients over existing treatments. A product eligible for accelerated approval may be approved on the basis of either 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, 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. 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, even if the effect on the surrogate or intermediate clinical endpoint occurs rapidly. Thus, accelerated approval has been used 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 studies to demonstrate a clinical or survival benefit. The accelerated approval pathway often also requires a sponsor's agreement to conduct additional post-approval confirmatory studies to verify and describe the product's clinical benefit. These confirmatory trials must be completed with due diligence and, in most 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.

Pediatric information

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

The Best Pharmaceuticals for Children Act, or BPCA, provides NDA holders a six-month extension of any exclusivity—patent or nonpatent—for a drug if certain conditions are met. Conditions for exclusivity include the FDA's determination that information relating to the use of a new drug in the pediatric population may produce health benefits in that population, the FDA making a written request for pediatric studies, and the applicant agreeing to perform, and reporting on, the requested studies within the statutory timeframe. Applications under the BPCA are treated as priority applications, with all of the benefits that designation confers.

Post-approval requirements

Once an NDA is approved, a product will be subject to certain post-approval requirements. For instance, the FDA closely regulates the post-approval marketing and promotion of drugs, including standards and regulations for direct-to-consumer advertising, off-label promotion, industry-sponsored scientific and educational activities and promotional activities involving the Internet. Drugs may be marketed only for the approved indications and in a manner consistent with the approved labeling.

Adverse event reporting and submission of periodic reports are required following FDA approval of an NDA. 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, drug manufacture, packaging and labeling procedures must continue to conform to current good manufacturing practices, or cGMPs, after approval. Drug manufacturers and certain of their subcontractors are required to register their establishments with the FDA and certain state agencies. Registration with FDA subjects entities to periodic unannounced inspections by the FDA, during which the Agency inspects manufacturing facilities to assess compliance with cGMPs. Accordingly, manufacturers must continue to expend time, money and effort in the areas of production and quality-control to maintain compliance with cGMPs. Regulatory authorities may withdraw product approvals or request product recalls if a company fails to comply with regulatory standards, if it encounters problems following initial marketing, or if previously unrecognized problems are subsequently discovered.

Rare pediatric disease designation and priority review vouchers

Under the Rare Pediatric Disease Priority Review Voucher program, the FDA may award a priority review voucher to the sponsor of an approved marketing application for a product that treats or prevents a rare pediatric disease. The voucher entitles the sponsor to priority review of one subsequent marketing application. A voucher may be awarded only for an approved rare pediatric disease product application. A rare pediatric disease product application is an NDA for a drug (in the case of a small molecule) that treats or prevents a serious or life-threatening disease in which the serious or life-threatening manifestations primarily affect individuals aged from birth to 18 years; in general, the disease must affect fewer than 200,000 such individuals in the United States; the NDA must be deemed eligible for priority review; the NDA must not seek approval for a different adult indication (i.e., for a different disease/condition); the drug must not contain an active ingredient that has been previously approved by the FDA; and the NDA must rely on clinical data derived from studies examining a pediatric population such that the approved product can be adequately labeled for the pediatric population. Before NDA approval, the FDA may designate a product in development as a product for a rare pediatric disease.

To receive a rare pediatric disease priority review voucher, a sponsor must notify the FDA, upon submission of the NDA, of its intent to request a voucher. If the FDA determines that the NDA is a rare pediatric disease product application, and if the NDA is approved, the FDA will award the sponsor of the NDA a voucher upon approval of the NDA. The FDA may revoke a rare pediatric disease priority review voucher if the product for which it was awarded is not marketed in the United States within 365 days of the product's approval. The voucher, which is transferable to another sponsor, may be submitted with a subsequent NDA or biologics license application, or BLA, and entitles the holder to priority review of the accompanying NDA or BLA. The sponsor submitting the priority review voucher must notify the FDA of its intent to submit the voucher with the NDA or BLA at least 90 days prior to submission of the NDA or BLA and must pay a priority review user fee in addition to any other required user fee. The FDA must take action on an NDA or BLA under priority review within six months of receipt of the NDA or BLA.

In December 2020, the program was reauthorized, allowing a product that is designated as a product for a rare pediatric disease prior to September 30, 2024, to be eligible to receive a rare pediatric disease priority review voucher upon approval of a qualifying NDA prior to September 30, 2026.

The Hatch-Waxman amendments

Orange Book Listing

Under the Drug Price Competition and Patent Term Restoration Act of 1984, commonly referred to as the Hatch Waxman Amendments, NDA applicants are required to identify to the FDA each patent whose claims cover the applicant's drug or approved method of using the drug. Upon approval of a drug, the applicant must update its listing of patents to the NDA in a timely fashion and each of the patents listed in the application for the drug is then published in the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations, commonly known as the Orange Book.

Drugs listed in the Orange Book can, in turn, be cited by potential generic competitors in support of approval of an abbreviated new drug application, or ANDA. An ANDA provides for marketing of a drug product that has the same active ingredient(s), strength, route of administration, and dosage form as the listed drug and has been shown through bioequivalence testing to be therapeutically equivalent to the listed drug. An approved ANDA product is considered to be therapeutically equivalent to the listed drug. Other than the requirement for bioequivalence testing, ANDA applicants are not required to conduct, or submit results of, preclinical or clinical tests to prove the safety or effectiveness of their drug product. Drugs approved under the ANDA pathway are commonly referred to as "generic equivalents" to the listed drug and can often be substituted by pharmacists under prescriptions written for the original listed drug pursuant to each state's laws on drug substitution.

The ANDA applicant is required to certify to the FDA concerning any patents identified for the reference listed drug in the Orange Book. Specifically, the applicant must certify to each patent in one of the following ways: (i) the required patent information has not been filed; (ii) the listed patent has expired; (iii) the listed patent has not expired but will expire on a particular date and approval is sought after patent expiration; or (iv) the listed patent is invalid or will not be infringed by the new product. A certification that the new product will not infringe the already approved product's listed patents, or that such patents are invalid, is called a Paragraph IV certification. For patents listed that claim an approved method of use, under certain circumstances the ANDA applicant may also elect to submit a section viii statement certifying that its proposed ANDA label does not contain (or carves out) any language regarding the patented method-of-use rather than certify to a listed method-of-use patent. If the applicant does not challenge the listed patents through a Paragraph IV certification, the ANDA application will not be approved until all the listed patents claiming the referenced product have expired. If the ANDA applicant has provided a Paragraph IV certification to the FDA, the applicant must also send notice of the Paragraph IV certification to the NDA holder and patentee(s) once the ANDA has been accepted for filing by the FDA (referred to as the "notice letter"). The NDA and patent holders may then initiate a patent infringement lawsuit in response to the notice letter. The filing of a patent infringement lawsuit within 45 days of the receipt of a Paragraph IV certification automatically prevents the FDA from approving the ANDA until the earlier of 30 months from the date the notice letter is received, expiration of the patent, the date a settlement order or consent decree is signed and entered by the court stating that the patent that is the subject of the Paragraph IV certification is invalid or not infringed, or a decision in the patent case that is favorable to the ANDA applicant.

The ANDA application also will not be approved until any applicable non-patent exclusivity listed in the Orange Book for the referenced product has expired. In some instances, an ANDA applicant may receive approval prior to expiration of certain non-patent exclusivity if the applicant seeks, and the FDA permits, the omission of such exclusivity-protected information from the ANDA prescribing information.

Exclusivity

Upon NDA approval of a new chemical entity, or NCE, which is a drug that contains no active moiety that has been approved by the FDA in any other NDA, that drug receives five years of marketing exclusivity during which the FDA cannot receive any ANDA seeking approval of a generic version of that drug unless the application contains a Paragraph IV certification, in which case the application may be submitted one year prior to expiration of the NCE exclusivity. If there is no listed patent in the Orange Book, there may not be a Paragraph IV certification, and, thus, no ANDA for a generic version of the drug may be filed before the expiration of the exclusivity period.

Certain changes to an approved drug, such as the approval of a new indication, the approval of a new strength, and the approval of a new condition of use, are associated with a three-year period of exclusivity from the date of approval during which the FDA cannot approve an ANDA for a generic drug that includes the change. In some instances, an ANDA applicant may receive approval prior to expiration of the three-year exclusivity if the applicant seeks, and the FDA permits, the omission of such exclusivity-protected information from the ANDA package insert.

Patent term extension

The Hatch Waxman Amendments permit a patent term extension as compensation for patent term lost during the FDA regulatory review process. Patent term extension, however, cannot extend the remaining term of a patent beyond a total of 14 years from the product's approval date. After NDA approval, owners of relevant drug patents may apply for the extension. The allowable patent term extension is calculated as half of the drug's testing phase (the time between IND application and NDA submission) and all of the review phase (the time between NDA submission and approval) up to a maximum of five years. The time can be reduced for any time the FDA determines that the applicant did not pursue approval with due diligence.

The USPTO, in consultation with the FDA, reviews and approves the application for any patent term extension or restoration. However, the USPTO may decide not to grant an extension because of, for example, failing to exercise due diligence during the testing phase or regulatory review process, failing to apply within applicable deadlines, failing to apply prior to expiration of relevant patents or otherwise failing to satisfy applicable requirements. Moreover, the applicable time period or the scope of patent protection afforded could be less than requested.

The total patent term after the extension may not exceed 14 years, and only one patent can be extended for any single product. The application for the extension must be submitted prior to the expiration of the patent, and for patents that might expire during the application phase, the patent owner may request an interim patent extension. An interim patent extension increases the patent term by one year and may be renewed up to four times. For each interim patent extension granted, the post-approval patent extension is reduced by one year. The director of the USPTO must determine that approval of the drug covered by the patent for which a patent extension is being sought is likely. Interim patent extensions are not available for a drug for which an NDA has not been submitted.

FDA regulation of companion diagnostics

If use of an in vitro diagnostic is essential to safe and effective use of a drug product, then the FDA generally will require approval or clearance of the diagnostic, known as a companion diagnostic, at the same time that the FDA approves the drug product. The FDA has generally required in vitro companion diagnostics intended to select the patients who will respond to cancer treatment to obtain a pre-market approval, or PMA, for that diagnostic simultaneously with approval of the drug. The review of these in vitro companion diagnostics in conjunction with the review of a cancer therapeutic involves coordination of review by the FDA's Center for Drug Evaluation and Research and by the FDA's Center for Devices and Radiological Health. Approval and clearance of a companion diagnostic also requires a high level of coordination between the drug manufacturer and device manufacturer, if different companies.

The PMA process, including the gathering of clinical and preclinical data and the submission to and review by the FDA, can take several years or longer. It involves a rigorous premarket review during which the applicant must prepare and provide the FDA with reasonable assurance of the device's safety and effectiveness and information about the device and its components regarding, among other things, device design, manufacturing and labeling. PMA applications are subject to a substantial application fee, which is typically increased annually.

In addition, PMAs must generally include the results from extensive preclinical and adequate and well-controlled clinical trials to establish the safety and effectiveness of the device for each indication for which FDA approval is sought. In particular, for a diagnostic, the applicant must demonstrate that the diagnostic has adequate sensitivity and specificity, has adequate specimen and reagent stability, and produces reproducible results when the same sample is tested multiple times by multiple users at multiple laboratories. As part of the PMA review, the FDA will typically inspect the manufacturer's facilities for compliance with the Quality System Regulation, or QSR, which imposes elaborate testing, control, documentation and other quality assurance requirements.

PMA approval is not guaranteed, and the FDA may ultimately respond to a PMA submission with a not approvable determination based on deficiencies in the application and require additional clinical trial or other data that may be expensive and time-consuming to generate and that can substantially delay approval. If the FDA's evaluation of the PMA application is favorable, the FDA typically issues an approvable letter requiring the applicant's agreement to specific conditions, such as changes in labeling, or specific additional information, such as submission of final labeling, in order to secure final approval of the PMA. If the FDA concludes that the applicable criteria have been met, the FDA will issue a PMA for the approved indications, which can be more limited than those originally sought by the applicant. The PMA can include post-approval conditions that the FDA believes necessary to ensure the safety and effectiveness of the device, including, among other things, restrictions on labeling, promotion, sale and distribution.

After a device is placed on the market, it remains subject to significant regulatory requirements. Medical devices may be marketed only for the uses and indications for which they are cleared or approved. Device manufacturers must also register their establishment(s), including payment of an annual establishment registration fee, and list their device(s) with the FDA. A medical device manufacturer's manufacturing processes and those of its suppliers are required to comply with the applicable portions of the QSR, which cover the methods and documentation of the design, testing, production, processes, controls, quality assurance, labeling, packaging and shipping of medical devices. Domestic facility records and manufacturing processes are subject to periodic unscheduled inspections by the FDA. The FDA also may inspect foreign facilities that export products to the United States.

Other healthcare laws

In addition to FDA restrictions on marketing of pharmaceutical products, several other types of state and federal laws have been applied to restrict certain general business and marketing practices in the pharmaceutical industry. These laws include anti-kickback, false claims, transparency and health information privacy laws and other healthcare laws and regulations.

The federal Anti-Kickback Statute prohibits, among other things, knowingly and willfully offering, paying, soliciting or receiving remuneration to induce, or in return for, purchasing, leasing, ordering or arranging for the purchase, lease or order of any healthcare item or service reimbursable under Medicare, Medicaid, or other federally financed healthcare programs. The Patient Protection and Affordable Care Act as amended by the Health Care and Education Reconciliation Act, collectively, the ACA, amended the intent element of the federal Anti-Kickback Statute so that a person or entity no longer needs to have actual knowledge of the statute or specific intent to violate it in order to commit a violation. This statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on the one hand and prescribers, purchasers and formulary managers, among others, on the other. Although there are a number of statutory exceptions and regulatory safe harbors protecting certain common activities from prosecution or other regulatory sanctions, the exceptions and safe harbors are drawn narrowly, and practices that involve remuneration intended to induce prescribing, purchases or recommendations may be subject to scrutiny if they do not qualify for an exception or safe harbor. Additionally, the ACA amended the federal Anti-Kickback Statute such that a violation of that statute can serve as a basis for liability under the federal civil False Claims Act.

Federal civil and criminal false claims laws, including the federal civil False Claims Act, prohibit any person or entity from knowingly presenting, or causing to be presented, a false claim for payment to the federal government, or knowingly making, or causing to be made, a false statement to have a false claim paid. This includes claims made to programs where the federal government reimburses, such as Medicare and Medicaid, as well as programs where the federal government is a direct purchaser, such as when it purchases off the Federal Supply Schedule. Pharmaceutical and other healthcare companies have been prosecuted under these laws for, among other things, allegedly inflating drug prices they report to pricing services, which in turn were used by the government to set Medicare and Medicaid reimbursement rates, and for allegedly providing free product to customers with the expectation that the customers would bill federal programs for the product. In addition, certain marketing practices, including off-label promotion, may also violate false claims laws. Most states also have statutes or regulations similar to the federal Anti-Kickback Statute and civil False Claims Act, which apply to items and services reimbursed under Medicaid and other state programs, or, in several states, apply regardless of the payor.

Other federal statutes pertaining to healthcare fraud and abuse include the civil monetary penalties statute, which prohibits, among other things, the offer or payment of remuneration to a Medicaid or Medicare beneficiary that the offeror or payor knows or should know is likely to influence the beneficiary to order or receive a reimbursable item or service from a particular supplier, and the additional federal criminal statutes created by the Health Insurance Portability and Accountability Act of 1996, or HIPAA, which prohibit, among other things, knowingly and willfully executing or attempting to execute a scheme to defraud any healthcare benefit program or obtain by means of false or fraudulent pretenses, representations or promises any money or property owned by or under the control of any healthcare benefit program in connection with the delivery of or payment for healthcare benefits, items or services.

In addition, HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009, or HITECH, and their respective implementing regulations, including the Final Omnibus Rule published on January 25, 2013, impose obligations on certain healthcare providers, health plans, and healthcare clearinghouses, known as covered entities, as well as their business associates and their subcontractors that perform certain services involving the storage, use or disclosure of individually identifiable health information, including mandatory contractual terms, with respect to safeguarding the privacy, security, and transmission of individually identifiable health information, and require notification to affected individuals and regulatory authorities of certain breaches of security of individually identifiable health information. HITECH increased the civil and criminal penalties that may be imposed against covered entities, business associates and possibly other persons, 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. In addition, many state laws govern the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and may not have the same effect, and often are not preempted by HIPAA.

Further, pursuant to the ACA, the Centers for Medicare & Medicaid Services, or CMS, issued a final rule that requires certain manufacturers of prescription drugs to collect and annually report information on certain payments or transfers of value to physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors) and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members. As of January 1, 2021, manufacturers must collect information regarding payments and other transfers of value to physician assistants, nurse practitioners, clinical nurse specialists, anesthesiologist assistants, certified registered nurse anesthetists, and certified nurse-midwives for reporting in the following year. The reported data is made available in searchable form on a public website on an annual basis. Failure to submit required information may result in civil monetary penalties.

We may also be subject to analogous state and foreign anti-kickback and false claims laws that may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental third-party payors, including private insurers, or that apply regardless of payor. In addition, several states now require prescription drug companies to report certain expenses relating to the marketing and promotion of drug products and to report gifts and payments to individual healthcare practitioners in those states. Other states prohibit various marketing-related activities, such as the provision of certain kinds of gifts or meals. Further, certain states require the posting of information relating to clinical studies and their outcomes. Some states require the reporting of certain drug pricing information, including information pertaining to and justifying price increases. In addition, certain states require pharmaceutical companies to implement compliance programs and/or marketing codes. Several additional states are considering similar proposals. Certain states and local jurisdictions also require the registration of pharmaceutical sales representatives. Additionally, we may also be subject to state and foreign laws governing the privacy and security of health information in some circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

Efforts to ensure that business arrangements with third parties comply with applicable state, federal, and foreign healthcare laws and regulations involve substantial costs. If a drug company's operations are found to be in violation of any such requirements, it may be subject to significant penalties, including civil, criminal and administrative penalties, damages, fines, disgorgement, imprisonment, the curtailment or restructuring of its operations, loss of eligibility to obtain approvals from the FDA, exclusion from participation in government contracting, healthcare reimbursement or other federal or state government healthcare programs, including Medicare and Medicaid, integrity oversight and reporting obligations, imprisonment, and reputational harm. Although effective compliance programs can mitigate the risk of investigation and prosecution for violations of these laws, these risks cannot be entirely eliminated. Any action for an alleged or suspected violation can cause a drug company

to incur significant legal expenses and divert management's attention from the operation of the business, even if such action is successfully defended.

U.S. healthcare reform

In the United States there have been, and continue to be, proposals by the federal government, state governments, regulators and third-party payors to control or manage the increased costs of health care and, more generally, to reform the U.S. healthcare system. The pharmaceutical industry has been a particular focus of these efforts and has been significantly affected by major legislative initiatives. For example, in March 2010, the ACA was enacted, which intended to broaden access to health insurance, reduce or constrain the growth of healthcare spending, enhance remedies against fraud and abuse, add new transparency requirements for the healthcare and health insurance industries, impose new taxes and fees on the health industry and impose additional health policy reforms, substantially changed the way healthcare is financed by both governmental and private insurers, and significantly impacts the U.S. pharmaceutical industry. The ACA, among other things, (i) subjected therapeutic biologics to potential competition by lower-cost biosimilars by creating a licensure framework for follow-on biologic products, (ii) prescribed a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs and therapeutic biologics that are inhaled, infused, instilled, implanted or injected, (iii) 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, (iv) established annual nondeductible fees and taxes on manufacturers of certain branded prescription drugs and therapeutic biologics, apportioned among these entities according to their market share in certain government healthcare programs, (v) established a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer 50% (now 70%) point of-sale discounts off negotiated prices of applicable brand drugs and therapeutic biologics to eligible beneficiaries during their coverage gap period, as a condition for the manufacturer's outpatient drugs and therapeutic biologics to be covered under Medicare Part D, (vi) 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, (vii) expanded the entities eligible for discounts under the Public Health program, (viii) created a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research, and (ix) established a Center for Medicare and Medicaid Innovation at CMS to test innovative payment and service delivery models to lower Medicare and Medicaid spending, potentially including prescription drug spending.

There have been executive, legislative and judicial efforts to modify, repeal, or otherwise invalidate all, or certain provisions of, the ACA. On June 17, 2021, the U.S. Supreme Court dismissed a challenge on procedural grounds that argued that the ACA is unconstitutional in its entirety because the "individual mandate" was repealed by Congress. Thus, the ACA will remain in effect in its current form. It is possible that the ACA will be subject to judicial or Congressional challenges in the future. It is uncertain how the U.S. Supreme Court ruling, other such litigation, or the healthcare measures of the Biden administration will impact the ACA and our business.

Other legislative changes have been proposed and adopted in the United States since the ACA was enacted to reduce healthcare expenditures. U.S. federal government agencies also currently face potentially significant spending reductions, which may further impact healthcare expenditures. On August 2, 2011, the Budget Control Act of 2011, among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. This includes aggregate reductions of Medicare payments to providers of 2% per fiscal year. These reductions went into effect on April 1, 2013 and, due to subsequent legislative amendments to the statute, including the BBA, will remain in effect through 2030, with the exception of a temporary suspension from May 1, 2020 through March 31, 2022. The Medicare reductions were phased back in starting with a 1% reduction in effect from April 1, 2022 to June 30, 2022 before increasing to the full 2% reduction after June 30, 2022. Moreover, on January 2, 2013, the American Taxpayer Relief Act of 2012 was signed into law, 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 federal spending is further reduced, anticipated budgetary shortfalls may also impact the ability of relevant agencies, such as the FDA or the National Institutes of Health, to continue to function at current levels. Amounts allocated to federal grants and contracts may be reduced or eliminated. These reductions may also

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 products we may develop.

Recently, 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 and enacted federal and state 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, the Trump administration used several means to propose or implement drug pricing reform, including through federal budget proposals, executive orders and policy initiatives. For example, on July 24, 2020 and September 13, 2020, the Trump administration of the United States announced several executive orders related to prescription drug pricing that sought to implement several of the administration's proposals. As a result, the FDA also released a final rule on September 24, 2020 providing guidance for states to build and submit importation plans for drugs from Canada. The Biden and Trump administrations both issued executive orders intended to favor government procurement from domestic manufacturers. In addition, the Trump administration issued an executive order specifically aimed at the procurement of pharmaceutical products, which instructed the federal government to develop a list of "essential" medicines and then buy those and other medical supplies that are manufactured, including the manufacture of the API, in the United States. It is unclear whether this executive order or something similar will be implemented by the Biden administration.

Further, on November 20, 2020, the U.S Department of Health and Human Services finalized a regulation removing safe harbor protection for price reductions from pharmaceutical manufacturers to plan sponsors under Part D, either directly or through pharmacy benefit managers, unless the price reduction is required by law. The rule also creates a new safe harbor for price reductions reflected at the point-of-sale, as well as a safe harbor for certain fixed fee arrangements between pharmacy benefit managers and manufacturers. Pursuant to court order, the removal and addition of the aforementioned safe harbors were delayed and recent legislation imposed a moratorium on implementation of the rule until January 1, 2026. This deadline was pushed back to January 1, 2027 by the Bipartisan Safer Communities Act. The Inflation Reduction Act of 2022, or the IRA, further delayed implementation of this rule to January 1, 2032. Additionally, on March 11, 2021, President Biden signed the American Rescue Plan Act of 2021 into law, which eliminates the statutory Medicaid drug rebate cap, currently set at 100% of a drug's average manufacturer price, for single source and innovator multiple source drugs, beginning January 1, 2024.

Most recently, in August 2022, President Biden signed into law the IRA, which will, among other things, allows the U.S. Department of Health and Human Services, or HHS, to negotiate the selling price of certain drugs and biologics that CMS reimburses under Medicare Part B and Part D, although this will only apply to high-expenditure single-source drugs that have been approved for at least seven years (11 years for biologics). The negotiated prices, which will first become effective in 2026, will be capped at a statutory ceiling price beginning in October 2023, penalize drug manufacturers that increase prices of Medicare Part B and Part D drugs at a rate greater than the rate of inflation. In addition, the law eliminates the "donut hole" under Medicare Part D beginning in 2025 by significantly lowering the beneficiary maximum out-of-pocket cost and requiring manufacturers to subsidize, through a newly established manufacturer discount program, 10% of Part D enrollees' prescription costs for brand drugs below the out-of-pocket maximum, and 20% once the out-of-pocket maximum has been reached. The IRA permits the Secretary of HHS to implement many of these provisions through guidance, as opposed to regulation, for the initial years. Manufacturers that fail to comply with the IRA may be subject to various penalties, including civil monetary penalties. The IRA also extends enhanced subsidies for individuals purchasing health insurance coverage in ACA marketplaces through plan year 2025. These provisions will take effect progressively starting in 2023, although they may be subject to legal challenges.

At the state level, legislatures are increasingly passing legislation and implementing 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.

We expect that additional state and federal healthcare reform measures will be adopted in the future.

Coverage and reimbursement

Patients in the United States and elsewhere generally rely on third-party payors to reimburse part or all of the costs associated with their prescription drugs. Accordingly, market acceptance of our drug products is dependent on the extent to which third-party coverage and reimbursement is available from government health administration authorities (including in connection with government healthcare programs, such as Medicare and Medicaid in the United States), private healthcare insurers and other healthcare funding organizations. Significant uncertainty exists as to the coverage and reimbursement status of any drug products for which we may obtain regulatory approval. Coverage decisions may not favor new drug products when more established or lower-cost therapeutic alternatives are already available. Patients are unlikely to use our products unless reimbursement is adequate to cover all or a significant portion of the cost of our drug products.

Coverage and reimbursement policies for drug products can differ significantly from payor to payor as there is no uniform policy of coverage and reimbursement for drug products among third-party payors in the United States. There may be significant delays in obtaining coverage and reimbursement as the process of determining coverage and reimbursement is often time-consuming and costly, which will require us to provide scientific and clinical support for the use of our products to each payor separately, with no assurance that coverage or adequate reimbursement will be obtained. It is difficult to predict at this time what government authorities and third-party payors will decide with respect to coverage and reimbursement for our drug products. Additionally, we may develop, either by ourselves or with collaborators, companion diagnostic tests for our product candidates for certain indications. We, or our collaborators, if any, will be required to obtain coverage and reimbursement for these tests separate and apart from the coverage and reimbursement we seek for our product candidates, once approved.

The market for our product candidates will depend significantly on access to third-party payors' drug formularies or lists of medications for which third-party payors provide coverage and reimbursement. Competition to be included in such formularies often leads to downward pricing pressures. In particular, third-party payors may refuse to include a particular reference listed drug in their formularies or otherwise restrict patient access to a reference listed drug when a less costly generic equivalent or other alternative is available.

The U.S. government, state legislatures and foreign governmental entities have shown significant interest in implementing cost containment programs to limit the growth of government-paid healthcare costs, including price controls, restrictions on reimbursement and coverage and requirements for substitution of generic products for branded prescription drugs. Adoption of government controls and measures and tightening of restrictive policies in jurisdictions with existing controls and measures, could exclude or limit our drugs products from coverage and limit payments for pharmaceuticals.

In addition, we expect that the increased emphasis on managed care and cost containment measures in the United States by third-party payors and government authorities will continue and will place pressure on pharmaceutical pricing and coverage. Coverage policies and third-party reimbursement rates may change at any time. Even if favorable coverage and reimbursement status is attained for one or more drug products for which we receive regulatory approval, less favorable coverage policies and reimbursement rates may be implemented in the future.

Employees and Human Capital Resources

We are committed to creating and maintaining a diverse, inclusive and safe work environment where our employees can bring their best selves to work each day. Our commitment to diversity extends through our recruitment, retention, learning and engagement and community partnerships. As part of our diversity, equity, inclusion and belonging strategy, we made an active decision to pursue opportunities for learning and engagement that bring people from different backgrounds together into conversation.

As of December 31, 2022, we had 121 full-time employees. Of these employees, 34 held Ph.D., Pharm.D. or M.D. degrees, and 72 were engaged in research, development and technical operations. From time to time, we also retain independent contractors to support our organization. Approximately half of our employees are based at our headquarters in Brisbane, California, with others working remotely. We have never experienced a work stoppage, none of our employees are represented by a labor union or covered by collective bargaining agreements, and we strive to attract and retain qualified employees in order to foster long-term working relationships.

We focus on employee development, engagement, and diversity and inclusion to identify, hire, develop, and retain the best talent. The principal purpose of our incentive share plan is to attract, retain and motivate selected employees, consultants and directors through the granting of incentive share-based compensation awards and cash-based performance bonus awards. We provide competitive compensation and benefits that are tailored specifically to the needs and requests of our employees and are designed to help us achieve our goals of attracting, hiring and retaining qualified personnel.

Facilities

Our principal executive office is located in Brisbane, California, where we lease approximately 12,000 square feet of office space. The lease expires in December 2024. There is no option to extend the lease term nor is there an option to terminate the lease prior to its expiration. We believe these facilities are sufficient to meet our ongoing needs and that, if we require additional space, we will be able to obtain additional facilities on commercially reasonable terms.

Legal Proceedings

From time to time, we may be involved in legal proceedings arising in the ordinary course of our business. We are not presently a party to any legal proceedings that, in the opinion of management, would have a material adverse effect on our business. Regardless of outcome, litigation can have an adverse impact on us due to defense and settlement costs, diversion of management resources, negative publicity and reputational harm, and other factors.

Corporate Information

We were formed as a limited liability company under the laws of the State of Delaware in November 2018, under the name Hero Therapeutics Holding Company, LLC. We subsequently changed our name to Day One Therapeutics Holding Company, LLC in December 2018 and to Day One Biopharmaceuticals Holding Company, LLC in March 2020. In connection with our initial public offering, we converted from a Delaware limited liability company to a Delaware corporation and changed our name to Day One Biopharmaceuticals, Inc, or the Conversion. Our principal executive offices are located at 2000 Sierra Point Parkway, Suite 501, Brisbane, CA 94005, and our telephone number is (650) 484-0899. Our website address is www.dayonebio.com.

Additional Information

Our Internet website address is http://www.dayonebio.com. On our website, we make available, free of charge, our annual, quarterly and current reports, including amendments to such reports, as soon as reasonably practicable after we electronically file such material with, or furnish such material to, the Securities and Exchange Commission, or the SEC. The SEC maintains a website at www.sec.gov that contains reports as well as other information regarding us and other companies that file materials with the SEC electronically.

Also available on our website is information relating to corporate governance at Day One and our board of directors, including our Corporate Governance Guidelines; our Code of Business Conduct and Ethics (for our directors, officers and employees), and our Board Committee Charters. We will provide any of the foregoing information without charge upon written request to our Corporate Secretary, Day One Biopharmaceuticals, Inc., 2000 Sierra Point Parkway, Suite 501, Brisbane, CA 94005.

We use our Investor Relations website (http://ir.dayonebio.com) as a means of disclosing material non-public information and for complying with our disclosure obligations under Regulation FD promulgated by the SEC. These disclosures are included in the “Press Releases” and “Events and Presentations” sections of our website. Accordingly, investors should monitor these portions of our website, in addition to following our press releases, SEC filings and public conference calls and webcasts.

The information contained on our website does not constitute, and shall not be deemed to constitute, a part of this Annual Report on Form 10-K, or any other report we file with, or furnish to, the SEC. Our references to the URLs for websites are intended to be inactive textual references only.

Item 1A. Risk Factors.

Investing in our common stock involves a high degree of risk. Before making your decision to invest in shares of our common stock, you should carefully consider the risks and uncertainties described below, together with the other information contained in this annual report, including our financial statements and the related notes and "Management's Discussion and Analysis of Financial Condition and Results of Operations." The risks and uncertainties described below are not the only ones we face. Additional risks and uncertainties that we are unaware of, or that we currently believe are not material, may also become important factors that affect us. We cannot assure you that any of the events discussed below will not occur. These events could have a material and adverse impact on our business, financial condition, results of operations and prospects. If that were to happen, the trading price of our common stock could decline, and you could lose all or part of your investment.

Summary of Risk Factors

Our business is subject to several risks and uncertainties, including those immediately following this summary. Some of these risks are:

- We have a limited operating history, have not completed any clinical trials beyond Phase 1, have no products approved for commercial sale and have not generated any revenue, which may make it difficult for investors to evaluate our current business and likelihood of success and viability.
- We have incurred significant net losses since our inception and have not generated any revenue. We expect to incur continued losses for the foreseeable future and may never achieve or maintain profitability.
- We are substantially dependent on the success of our lead product candidate, tovorafenib (DAY101), which is currently in clinical development and has not completed a pivotal trial.
- Our ability to generate revenue and achieve profitability depends significantly on our ability to achieve several objectives relating to the discovery or identification, development and commercialization of our product candidates.
- We will require substantial additional capital to finance our operations and achieve our goals. If we are unable to raise capital when needed or on terms acceptable to us, we may be forced to delay, reduce or eliminate our research or product development programs, any future commercialization efforts or other operations.
- Clinical trials are very expensive, time-consuming and difficult to design and implement, and involve uncertain outcomes. Furthermore, results of earlier preclinical studies and clinical trials may not be predictive of results of future preclinical studies or clinical trials. Our product candidates may not have favorable results in later clinical trials, if any, or receive regulatory approval.
- We rely on data from an investigator-initiated Phase 2 clinical trial in our regulatory filings and we do not control the trial operations or reporting of the results.
- If we fail to demonstrate safety and efficacy to our stakeholders, our reputation may be harmed and our business will suffer.
- The development and commercialization of pharmaceutical products are subject to extensive regulation, and we may not obtain regulatory approvals for tovorafenib (DAY101), pimasertib or any future product candidates, on a timely basis or at all.
- The manufacture of our product candidates is complex. Our third-party manufacturers may encounter difficulties in production, which could delay or entirely halt their ability to supply our product candidates for clinical trials or, if approved, for commercial sale.
- Our future success depends on our ability to retain our executive officers and key employees and to attract, retain and motivate qualified personnel and manage our human capital.
- We will need to grow the size and capabilities of our organization, and we may experience difficulties in managing this growth.

- If we are unable to obtain and maintain patent protection or other necessary rights for our products and technology, or if the scope of the patent protection obtained is not sufficiently broad or our rights under licensed patents are not sufficiently broad, our competitors could develop and commercialize products and technology similar or identical to ours, and our ability to successfully commercialize our products and technology may be adversely affected.

Risks Related to Our Financial Position and Need for Additional Capital

We have a limited operating history, have not completed any clinical trials beyond Phase 1, have no products approved for commercial sale and have not generated any revenue, which may make it difficult for investors to evaluate our current business and likelihood of success and viability.

We are a clinical-stage biopharmaceutical company with a limited operating history upon which you can evaluate our business and prospects. We commenced operations in 2018, have no products approved for commercial sale and have never generated any revenue. Investment in drug development is a highly speculative undertaking and involves a substantial degree of risk. To date, we have devoted substantially all of our resources to identifying, acquiring and developing our product candidates and building our pipeline, organizing and staffing our company, business planning, establishing and maintaining our intellectual property portfolio, establishing arrangements with third parties for the manufacture of our product candidates, raising capital and providing general and administrative support for these operations.

Since our inception, we have focused substantially all of our efforts and financial resources on the clinical development of our lead product candidate, tovorafenib (DAY101), initially for relapsed or progressive low-grade gliomas, or pLGGs, and our other current product candidate, pimasertib, an orally available small molecule inhibitor of MEK kinase, which we intend to use in combination with tovorafenib (DAY101) for the treatment of RAS- and RAF-dependent tumors. To date, we have financed our operations primarily through the sale and issuance of redeemable convertible preferred shares, convertible notes, and the completion of our initial public offering, or IPO, and follow-on public offerings of our common stock.

We have not yet demonstrated an ability to successfully complete any clinical trials beyond Phase 1, obtain marketing approvals, manufacture a commercial-scale product or arrange for a third party to do so on our behalf, or conduct sales and marketing activities necessary for successful product commercialization. As a result, it may be more difficult for you to accurately predict our likelihood of success and viability than it could be if we had a longer operating history.

In addition, we may encounter unforeseen expenses, difficulties, complications, delays and other known and unknown factors and risks frequently experienced by clinical-stage biopharmaceutical companies in rapidly evolving fields. We also may need to transition from a company with a research and development focus to a company capable of supporting commercial activities. We have not yet demonstrated an ability to successfully overcome such risks and difficulties, or to make such a transition. If we do not adequately address these risks and difficulties or successfully make such a transition, our business will suffer.

We have incurred significant net losses since our inception and have not generated any revenue. We expect to incur continued losses for the foreseeable future and may never achieve or maintain profitability.

We have incurred significant net losses in each reporting period since our inception, have not generated any revenue to date and have financed our operations principally through private placements of our redeemable convertible preferred shares, our convertible notes, the completion of our IPO and follow-on offerings of our common stock. For the years ended December 31, 2022 and 2021, we reported a net loss of $142.2 million and $72.8 million, respectively. We had an accumulated deficit of $269.7 million as of December 31, 2022. We expect to incur increasing levels of operating losses for the foreseeable future, particularly as we advance tovorafenib (DAY101) and pimasertib through clinical development. Our prior losses, combined with expected future losses, have had, and will continue to have, an adverse effect on our stockholders' equity and working capital. We expect our research and development expenses to significantly increase in connection with our additional planned clinical trials for our lead product candidate and other product candidates, including our ongoing pivotal Phase 2 FIREFLY-1 trial for tovorafenib (DAY101), our ongoing pivotal Phase 3 FIREFLY-2 trial of tovorafenib (DAY101) as a potential frontline therapy in pLGG, our ongoing Phase 1b/2 FIRELIGHT-1 umbrella master trial of tovorafenib (DAY101) in adult RAS/RAF-altered solid tumors as a monotherapy and in combination with pimasertib, and development of

and subsequent Investigational New Drug Applications, or INDs, for any future product candidates we may choose to pursue. In addition, if we obtain marketing approval for tovorafenib (DAY101), pimasertib, or another product candidate, we will incur significant sales, marketing and outsourced manufacturing expenses in connection with the commercialization of tovorafenib (DAY101), pimasertib, or such other product candidate. We have also incurred, and will continue to incur, additional costs associated with operating as a public company.

As a result, we expect to continue to incur significant and increasing net losses for the foreseeable future. Because of the numerous risks and uncertainties associated with developing pharmaceutical products, we are unable to predict the extent of any future losses or when we will become profitable, if at all. Even if we do become profitable, we may not be able to sustain or increase our profitability on a quarterly or annual basis. In addition, we expect our financial condition and operating results to fluctuate significantly from quarter-to-quarter and year-to-year due to a variety of factors, many of which are beyond our control. Accordingly, you should not rely upon the results of any quarterly or annual periods as indications of future operating performance.

We are substantially dependent on the success of our lead product candidate, tovorafenib (DAY101), which is currently in clinical development and has not completed a pivotal trial.

Our future success is highly dependent on our ability to timely complete successful clinical trials, obtain regulatory approval for, and then successfully commercialize, our product candidates. We are early in our development efforts and our lead product candidate, tovorafenib (DAY101), is currently in a pivotal Phase 2 clinical trial. Our other current product candidate, pimasertib, is in an earlier stage of development. We currently have no products that are approved for sale in any jurisdiction. There can be no assurance that tovorafenib (DAY101), pimasertib or any future product candidates we develop, if any, will achieve success in their clinical trials or obtain regulatory approval.

Our ability to generate product revenue, which we do not expect will occur in the near future, if ever, will depend heavily on the successful development and eventual commercialization of our lead product candidate, tovorafenib (DAY101). The success of tovorafenib (DAY101) will depend on several factors, including the following:

- successful and timely completion of current and future clinical trials resulting in attractive, competitive target product profiles, including our frontline pivotal Phase 3 FIREFLY-2 trial;
- the results of our ongoing clinical trial for tovorafenib (DAY101) and Phase 1b/2 umbrella master trial of tovorafenib (DAY101) as a monotherapy and in combination with pimasertib meeting clinical endpoints;
- acceptance of NDAs by the U.S. Food and Drug Administration, or FDA, or other similar clinical trial applications from foreign regulatory authorities for our future clinical trials for our pipeline product candidates;
- timely and successful enrollment of patients in, and completion of, clinical trials with favorable results;
- demonstration of safety, efficacy and acceptable risk-benefit profiles of our product candidates to the satisfaction of the FDA and foreign regulatory agencies and attractiveness of our product candidates to physicians, patients, advocates, payors and caregivers;
- our ability, or that of our collaborators, to develop and obtain clearance or approval of companion diagnostics, on a timely basis, or at all, and an adequate supply of these companion diagnostics and access to these companion diagnostics that outpaces demand;
- receipt and related terms of marketing approvals from applicable regulatory authorities, including the completion of any required post-marketing studies or trials and available funding to perform any post-marketing commitments;
- raising additional funds necessary to complete clinical development of and commercialize our product candidates;
- obtaining and maintaining patent, trade secret and other intellectual property protection and regulatory exclusivity for our product candidates;

- making arrangements with third-party manufacturers, or establishing manufacturing capabilities, for both clinical and commercial supplies of our product candidates and ensuring a resilient, effective supply chain that produces supply that outpaces demand;
- developing and implementing marketing and reimbursement strategies, as well as adequate demand forecasts for supply and sales planning;
- establishing sales, marketing and distribution capabilities and launching commercial sales of our products, if and when approved, whether alone or in collaboration with others in a market where promotional sales approaches are rapidly moving to digital platforms and rep access to major institutions remains uncertain;
- acceptance of our products, if and when approved, by patients, the medical community and third-party payors underpinned by adequate health economic data and a meaningful value proposition;
- effectively competing with other therapies, including those that have not yet entered the market;
- effectively competing with other companies in the pharmaceutical and biotechnology industries, which are characterized by rapidly advancing technologies, intense competition and a strong emphasis on proprietary and novel products and product candidates;
- obtaining and maintaining third-party payor coverage and adequate reimbursement in both public and private payor spaces across multiple countries;
- obtaining appropriate support from patient advocacy organizations;
- effectively shaping the market in the early years following launch to help providers understand a new way of thinking about treating these patients;
- addressing any delays in our ongoing and planned clinical trials resulting from factors related to any macroeconomic conditions, major natural disaster or significant political event, including inflation and changes in interest rates, the war in Ukraine and the ongoing COVID-19 pandemic;
- protecting and enforcing our rights in our intellectual property portfolio; and
- maintaining a continued acceptable safety profile of the products following approval.

Many of these factors are beyond our control, and it is possible that none of our product candidates will ever obtain regulatory approval even if we expend substantial time and resources seeking such approval. If we do not achieve one or more of these factors in a timely manner or at all, we could experience significant delays or an inability to successfully commercialize our product candidates, which would materially harm our business.

Our ability to generate revenue and achieve profitability depends significantly on our ability to achieve several objectives relating to the discovery or identification, development and commercialization of our product candidates.

Our business depends entirely on the successful discovery or identification, development and commercialization of product candidates. We have no products approved for commercial sale and do not anticipate generating any revenue from product sales for the next 12 months, if ever. We do not expect to generate significant revenue unless and until we obtain marketing approval for, and begin to sell, tovorafenib (DAY101), pimasertib, or another product candidate. Our ability to generate revenue and achieve profitability depends on several factors, including, but not limited to, our ability to:

- complete a successful pivotal Phase 2 FIREFLY-1 trial with tovorafenib (DAY101) that achieves a competitive, clinically meaningful and generally well-tolerated target product profile;
- complete a successful pivotal Phase 3 FIREFLY-2 trial with tovorafenib (DAY101) that achieves a competitive, clinically meaningful and generally well-tolerated target product profile in front-line pLGG;
- complete a successful Phase 1b/2 FIRELIGHT-1 umbrella master trial of tovorafenib (DAY101) as a monotherapy and in combination with pimasertib in patients 12 years and older with tumors having activated RAF signaling;

- initiate and successfully complete all safety, pharmacokinetic and other studies required to obtain U.S. and foreign marketing approval for tovorafenib (DAY101) as a treatment for patients with pLGGs;
- initiate and complete successful later-stage clinical trials that meet their clinical endpoints;
- obtain favorable results from our clinical trials and apply for and obtain marketing approval for tovorafenib (DAY101) and pimasertib from applicable regulatory authorities, including NDAs, from the FDA, and maintaining such approvals;
- establish licenses, collaborations or strategic partnerships that allow for the commercialization of our product candidates and/or may increase the value of our programs;
- establish and maintain viable supply and manufacturing relationships with third parties that can provide adequate, in both amount and quality, products and services to support clinical development and meet the market demand for our product candidates, if approved;
- successfully commercialize tovorafenib (DAY101), pimasertib, and any future product candidates we may develop, if approved, by building a sales force or entering into collaborations with third parties;
- satisfy any required post-marketing approval commitments to applicable regulatory authorities;
- maintain a continued acceptable safety profile following any marketing approval of our product candidates;
- identify, assess and develop new product candidates;
- establish and maintain patent and trade secret protection or regulatory exclusivity for our product candidates;
- maintain an acceptable safety profile of our products, including tovorafenib (DAY101) and pimasertib;
- obtain, maintain, protect and defend our intellectual property portfolio;
- address any competing therapies and technological and market developments;
- achieve market acceptance of tovorafenib (DAY101) or pimasertib and our other successful product candidates, if any, with patients, the medical community and third-party payors, both in the United States and internationally; and
- attract, hire and retain qualified personnel.

To become and remain profitable, we must succeed in designing, developing and eventually commercializing products that generate significant revenue. This will require us to be successful in a range of challenging activities, including completing clinical trials for our product candidates, designing and/or acquiring additional product candidates, establishing arrangements with third parties for the manufacture of clinical supplies of our product candidates, obtaining marketing approval for our product candidates and manufacturing, retaining intellectual property or marketing exclusivity and marketing and selling any products for which we may obtain marketing approval, if any. We are in the earlier stages of most of these activities. We may never succeed in these activities and, even if we do, may never generate revenues that are significant enough to achieve profitability.

In cases where we are successful in obtaining regulatory approval to market one or more of our product candidates, our revenue will be dependent, in part, upon the size of the markets in the territories for which we gain regulatory approval, the accepted price for the product, the duration of treatment that physicians believe is appropriate for our product, the speed of physician adoption, the ability to obtain coverage and reimbursement, and whether we own the commercial rights for that territory. If the number of our addressable patients is not as significant as we estimate, the indication approved by regulatory authorities is narrower than we expect, or the treatment population is narrowed by competition, physician choice, payor decisions or treatment guidelines, we may not generate significant revenue from sales of such products, even if approved.

If we decide to or are required by the FDA or regulatory authorities in other jurisdictions to perform studies or clinical trials in addition to, those currently expected, or to modify ongoing or planned clinical trials, or if there are any delays in establishing appropriate manufacturing arrangements for, in initiating or completing our current and planned clinical trials for, or in the development of, any of our product candidates, our expenses could increase significantly and profitability could be further delayed.

Our failure to become and remain profitable could depress the value of our company and could impair our ability to raise capital, expand our business, maintain our research and development efforts, diversify our product offerings or even continue our operations. A decline in the value of our company could also cause you to lose all or part of your investment.

We will require substantial additional capital to finance our operations and achieve our goals. If we are unable to raise capital when needed or on terms acceptable to us, we may be forced to delay, reduce or eliminate our research or product development programs, any future commercialization efforts or other operations.

Developing pharmaceutical products, including conducting preclinical studies and clinical trials, is a very time-consuming, expensive and uncertain process that takes years to complete. Our operations have consumed substantial amounts of cash since inception, and we expect our expenses to increase substantially in connection with our ongoing activities, particularly as we advance our lead product candidate, tovorafenib (DAY101), pimasertib, and any future product candidates through clinical development. We expect increased expenses as we continue our research and development, initiate additional clinical trials, seek to expand our product pipeline, seek marketing approval for our lead programs and future product candidates, if any, and invest in our organization. In addition, if we obtain marketing approval for any of our product candidates, we expect to incur significant commercialization expenses related to product manufacturing, marketing, sales and distribution. Furthermore, we have incurred and will continue to incur additional costs associated with operating as a public company, such as acquiring and retaining experienced personnel, developing new information technology systems, and other costs associated with being a public company. Also, we expect to experience ongoing and additional costs related to preparing and filing patent applications, maintaining our intellectual property and potentially expanding our office facilities. Accordingly, we will need to obtain substantial additional funding in connection with our continuing operations.

Adequate additional financing may not be available to us on favorable terms, or at all. 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. If we are unable to raise capital when needed or on favorable terms, we could be forced to delay, reduce or eliminate our research and development programs, our commercialization plans or other operations. Our ability to raise capital may be adversely impacted by potential worsening global economic conditions and disruptions to and volatility in the credit and financial markets in the United States and worldwide resulting from inflation, changes in interest rates, geopolitical instability, including the war in Ukraine, the ongoing COVID-19 pandemic or otherwise.

We had $342.3 million in cash, cash equivalents and short-term investments as of December 31, 2022. We believe that our existing cash, cash equivalents and short-term investments, will enable us to fund our operating expenses, and capital expenditure requirements into 2025. We have based this estimate on assumptions that may prove to be wrong, and we could use our capital resources sooner than we currently expect. Changes beyond our control may occur that would cause us to use our available capital before that time, including changes in and progress of our drug development activities and changes in regulation. Our future capital requirements will depend on many factors, including:

- the progress, timing and results of preclinical studies and clinical trials for our current or any future product candidates;
- the extent to which we develop, in-license or acquire other pipeline product candidates or technologies;
- the number and development requirements of current or future product candidates that we may pursue, and other indications for our current product candidates that we may pursue;
- the costs, timing and outcome of obtaining regulatory approvals of our current or future product candidates or the modification of ongoing or planned clinical trials, and any companion diagnostics we may pursue;
- the scope and costs of making arrangements with third-party manufacturers, or establishing manufacturing capabilities, for both clinical and commercial supplies of our current or future product candidates;
- the costs involved in growing our organization to the size needed to allow for the research, development and potential commercialization of our current or future product candidates;

- to the extent we pursue strategic collaborations, including collaborations to commercialize tovorafenib (DAY101), pimasertib, or any of our future pipeline product candidates, if any, our ability to establish and maintain collaborations on favorable terms, if at all, as well as the timing and amount of any milestone or royalty payments we are required to make or are eligible to receive under such collaborations or our current licenses;
- the cost associated with commercializing any approved product candidates, including establishing sales, marketing, market access and distribution capabilities;
- the cost associated with completing any post-marketing studies or trials required by the FDA or other regulatory authorities;
- the revenue, if any, received from commercial sales of tovorafenib (DAY101), pimasertib or any of our future product candidates if any are approved, or any future pipeline product candidates that receive marketing approval;
- the costs of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending intellectual property-related claims that we may become subject to, including any litigation costs and the outcome of such litigation; and
- the costs associated with potential product liability claims, including the costs associated with obtaining insurance against such claims and with defending against such claims.

We will require additional capital to complete our planned clinical development programs for our current product candidates to obtain regulatory approval, and we anticipate needing to raise additional capital to complete the development of and commercialize our product candidates. Our ability to raise additional funds will depend on financial, economic and market conditions and other factors, over which we may have no or limited control. If adequate funds are not available on commercially acceptable terms when needed, we may be forced to delay, reduce or terminate the development or commercialization of all or part of our research programs or product candidates or we may be unable to take advantage of future business opportunities. Furthermore, any additional capital-raising efforts may divert our team's attention from their day-to-day activities, which may adversely affect our business, including our ability to develop and commercialize our current and future product candidates, if approved. Changing circumstances, some of which may be beyond our control, could cause us to consume capital significantly faster than we currently anticipate, and we may need to seek additional funds sooner than planned.

We will be required to obtain further funding through public or private equity financings, debt financings, collaborative agreements, licensing arrangements or other sources of financing, which may dilute our stockholders or restrict our operating activities. We do not have any committed external source of funds. In June 2022, we entered into an equity distribution agreement with Piper Sandler & Co. and JonesTrading Institutional Services LLC, as sales agents, relating to the issuance and sale of shares of our common stock for an aggregate offering price of up to $150.0 million under an at-the-market offering program, or 2022 ATM. To the extent that we raise additional capital through the sale of equity or convertible debt securities, including pursuant to our 2022 ATM, each investor's ownership interests will be diluted, and the terms may include liquidation or other preferences that adversely affect each investor's rights as a stockholder. Debt financing may result in imposition of debt covenants, increased fixed payment obligations or other restrictions that may affect our business. If we raise additional funds through upfront payments or milestone payments pursuant to strategic collaborations with third parties, we may have to relinquish valuable rights to our product candidates or grant licenses on terms that are not favorable to us. Our ability to raise additional funds may be adversely impacted by potential worsening global economic conditions and disruptions to and volatility in the credit and financial markets in the United States and worldwide resulting from inflation, changes in interest rates, geopolitical instability, including the war in Ukraine, the ongoing COVID-19 pandemic or otherwise.

Our failure to raise capital as and when needed or on acceptable terms would have a negative impact on our financial condition and our ability to pursue our business strategy, and we may have to delay, reduce the scope of, suspend or eliminate one or more of our research or drug development programs, clinical trials or future commercialization efforts.

Risks Related to Development and Commercialization of Our Product Candidates

Clinical trials are very expensive, time-consuming and difficult to design and implement, and involve uncertain outcomes. Furthermore, results of earlier preclinical studies and clinical trials may not be predictive of results of future preclinical studies or clinical trials. Our product candidates may not have favorable results in later clinical trials, if any, or receive regulatory approval.

The risk of failure for our product candidates is high. It is impossible to predict when or if any of our product candidates will prove effective or safe in humans or will receive regulatory approval. To obtain the requisite regulatory approvals to market and sell any of our product candidates, we must demonstrate through extensive preclinical studies and clinical trials that our product candidates are safe and effective in humans for use in each target indication. Clinical testing is expensive and can take many years to complete, and the outcome is inherently uncertain. Failure can occur at any time during the clinical trial process.

In addition, the results of preclinical studies and earlier clinical trials may not be predictive of the results of later-stage preclinical studies or clinical trials. We have limited clinical data for our product candidates. Product candidates in later stages of clinical trials may fail to show similar or desired safety and efficacy traits despite having progressed through preclinical and earlier stage clinical trials.

In some instances, there can be significant variability in safety or efficacy results between different clinical trials of the same product candidate due to numerous factors, including changes in clinical trial procedures set forth in protocols, differences in the size and type of the patient populations, adherence to the dosing regimen and other clinical trial protocols, and the rate of discontinuation among clinical trial participants. If we fail to produce positive results in our planned clinical trials of any of our product candidates, the development timeline and regulatory approval and commercialization prospects for our product candidates, and, correspondingly, our business and financial prospects, would be materially and adversely affected.

We rely on data from an investigator-initiated Phase 2 clinical trial in our regulatory filings and we do not control the trial operations or reporting of the results.

The pivotal Phase 2 FIREFLY-1 trial for our lead product candidate, tovorafenib (DAY101), is run as an investigator-initiated, multi-center trial in patients with relapsed/refractory pLGG that is being conducted by the Dana Farber Cancer Institute in collaboration with the Pacific Pediatric Neuro-Oncology Consortium, or PNOC. The last data reported from this trial was in January 2023. It is possible that additional data, when reported, will not demonstrate similar results. We have no control over the timing of such clinical data announcements. In addition, although we expect that our pivotal Phase 2 FIREFELY-1 trial in pLGG will provide a sufficient dataset to support approval based on preliminary discussions with regulatory agencies, we cannot assure you that the FDA will not require data from additional patients or additional follow-up data from existing patients to support approval. In later-stage clinical trials, we will likely be subject to more rigorous statistical analyses than in completed earlier stage clinical trials. A number of companies in the pharmaceutical industry have suffered significant setbacks in later-stage clinical trials due to lack of efficacy or adverse safety profiles, notwithstanding promising results in earlier trials, and we cannot be certain that we will not face similar setbacks. Moreover, preclinical and clinical data are often susceptible to varying interpretations and analyses, and many companies that have believed their product candidates performed satisfactorily in preclinical studies and clinical trials have nonetheless failed to obtain marketing approval of their products.

Furthermore, we do not control the design or administration of investigator-sponsored trials, nor the submission or approval of any IND or foreign equivalent required to conduct these trials, and the investigator-sponsored trials could, depending on the actions of such third parties, jeopardize the validity of the clinical data generated, identify significant concerns with respect to our product candidates that could impact our findings or clinical trials, and adversely affect our ability to obtain marketing approval from the FDA or other applicable regulatory authorities. To the extent the results of this or other investigator-sponsored trials are inconsistent with, or different from, the results of our planned company-sponsored trials or raise concerns regarding our product candidates, the FDA or a foreign regulatory authority may question the results of the company-sponsored trial, or subject such results to greater scrutiny than it otherwise would. In these circumstances, the FDA or such foreign regulatory authorities may require us to obtain and submit additional clinical data, which could delay clinical development or marketing approval of our product candidates. While investigator-sponsored initiated trials could be useful to inform our own clinical development efforts, we do not control the data or timing of data releases for investigator-sponsored trials, and there

is no guarantee that we will be able to use the data from these trials to form the basis for regulatory approval of our product candidates.

In addition, some patients who receive access to drugs prior to their commercial approval through compassionate use, expanded access programs or right to try access, collectively referred to as compassionate use programs, have life-threatening illnesses and have exhausted all other available therapies. The risk for serious adverse events in this patient population is high, which, if those adverse events are determined to be drug-related, could have a negative impact on the safety profile of our drug candidates if we were to provide them to these patients, which could cause significant delays or an inability to successfully commercialize our drug candidates and materially harm our business. If we were to provide patients with any of our drug candidates under a compassionate use program, our supply capabilities may limit the number of patients who are able to enroll in the program and we may in the future need to restructure or pause any compassionate use program in order to enroll sufficient numbers of patients in our controlled clinical trials required for regulatory approval and successful commercialization of our drug candidates, which could prompt adverse publicity or other disruptions related to current or potential participants in such programs.

Our clinical trials may fail to adequately demonstrate the safety and efficacy of any of our product candidates, which would prevent or delay development, regulatory approval and commercialization.

Before obtaining marketing approval from the FDA or comparable foreign regulatory authorities for the sale of our current product candidates, we must demonstrate through lengthy, complex and expensive clinical trials that our product candidates are both safe and effective for use in each target indication. Clinical testing is expensive, difficult to design and implement, can take many years to complete and its ultimate outcome is uncertain. Failure can occur at any time during the clinical trial processes, and, because our product candidates are in earlier stages of development, there is a high risk of failure and we may never succeed in developing marketable products.

We may experience numerous unforeseen events during, or as a result of, clinical trials that could delay or prevent receipt of marketing approval or our ability to commercialize our product candidates, including:

- failure of our product candidates in clinical trials to demonstrate safety and efficacy;
- a failure to demonstrate that the dose for a product candidate has been optimized;
- failure of our product candidates in clinical trials to demonstrate important functional, quality, or patient-reported outcomes;
- changes in the competitive landscape preventing marketing authorization in one or several subsets studied in our programs, including in relapsed or front-line pLGG;
- receipt of feedback from regulatory authorities that requires us to modify the design of our clinical trials;
- negative or inconclusive clinical trial results that may require us to conduct additional clinical trials or abandon certain research and/or drug development programs;
- the number of patients required for clinical trials being larger than anticipated, enrollment in these clinical trials being slower than anticipated or participants dropping out of these clinical trials at a higher rate than anticipated;
- third-party contractors failing to comply with regulatory requirements or meet their contractual obligations to us in a timely manner, or at all;
- the suspension or termination of our clinical trials for various reasons, including non-compliance with regulatory requirements or a finding that our product candidates have undesirable side effects or other unexpected characteristics or risks;
- the cost of clinical trials of our product candidates being greater than anticipated;
- the supply or quality of our product candidates or other materials necessary to conduct clinical trials of our product candidates being insufficient or inadequate;
- regulators revising the requirements for approving our product candidates; and

- receipt of feedback from regulatory authorities that would require us to include data from additional patients or longer term efficacy and safety data.

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 in a timely manner, if the results of these trials or tests are not positive or are only modestly positive or if there are safety concerns, we may incur unplanned costs, be delayed in seeking and obtaining marketing approval, if we receive such approval at all, receive more limited or restrictive marketing approval, be subject to additional post-marketing testing requirements or have the drug removed from the market after obtaining marketing approval.

Our product candidates are initially targeted towards the pediatric population, for which safety concerns may be particularly scrutinized by regulatory agencies. Trials involving pediatric populations can be difficult to conduct, can be quite costly and, like other clinical trials, may not yield the anticipated results. In addition, pediatric studies are more dependent on a smaller number of specialized clinical trial sites, which in turn can limit site availability and make the trials more expensive to conduct. In addition, as interest in pediatric indications grows as a result of the Research to Accelerate Cures and Equity (RACE) for Children Act and other market forces, trial recruitment may become even more difficult due to competition for eligible patients. Moreover, it may be challenging to ensure that pediatric or adolescent patients adhere to clinical trial protocols. Our inability to enroll a sufficient number of pediatric patients for our clinical trial could result in significant delays, require us to abandon one or more clinical trials altogether, impact our ability to raise additional capital and delay or prevent our ability to obtain necessary regulatory approvals for any drug product candidate.

Additionally, if the results of our clinical trials are inconclusive or if there are safety concerns or serious adverse events associated with our product candidates, we may:

- be delayed in obtaining marketing approval, if at all;
- obtain approval for indications or patient populations that are not as broad as intended or desired or may have restricted duration expectations or guidance;
- obtain approval with labeling that includes significant use or distribution restrictions or safety warnings;
- be subject to additional post-marketing testing requirements;
- be required to perform additional clinical trials to support approval or be subject to additional post-marketing testing requirements;
- have regulatory authorities withdraw, or suspend, their approval of the drug or impose restrictions on its distribution in the form of a modified risk evaluation and mitigation strategy, or REMS;
- be subject to the addition of labeling statements, such as warnings or contraindications;
- be subject to civil or criminal investigations and litigation; or
- experience damage to our reputation.

Our drug development costs will also increase if we experience delays in testing or obtaining marketing approvals. Also, delays in obtaining marketing approval may increase commercialization costs if the competitive environment becomes more intense prior to market entry. We do not know whether any of our preclinical studies or clinical trials will begin as planned, need to be restructured or be completed on schedule, if at all.

Further, we, the FDA or an institutional review board, or IRB, may suspend our clinical trials at any time if it appears that we or our collaborators are failing to conduct a trial in accordance with regulatory requirements, including the FDA's current Good Clinical Practice, or GCP, regulations, that we are exposing participants to unacceptable health risks, or if the FDA finds deficiencies in our investigational NDAs or the conduct of these trials. Therefore, we cannot predict with any certainty the schedule for commencement and completion of future clinical trials. Further, conducting clinical trials in foreign countries, as we may do for our product candidates, presents additional risks that may delay completion of our clinical trials. These risks include the failure of enrolled patients in foreign countries to adhere to clinical protocol as a result of differences in healthcare services or cultural customs, managing additional administrative burdens associated with foreign regulatory schemes, as well as political and economic risks relevant to such foreign countries.

Moreover, principal investigators for our clinical trials may serve as scientific advisors or consultants to us from time to time and receive compensation in connection with such services. Under certain circumstances, we may be required to report some of these relationships to the FDA or comparable foreign regulatory authorities. The FDA or comparable foreign regulatory authority may conclude that a financial relationship between us and a principal investigator has created a conflict of interest or otherwise affected interpretation of the study. The FDA or comparable foreign regulatory authority may therefore question the integrity of the data generated at the applicable clinical trial site and the utility of the clinical trial itself may be jeopardized. This could result in a delay in approval, or rejection, of our marketing applications by the FDA or comparable foreign regulatory authority, as the case may be, and may ultimately lead to the denial of marketing approval of one or more of our product candidates.

In addition, many of the factors that cause, or lead to, termination or suspension of, or a delay in the commencement or completion of, clinical trials may also ultimately lead to the denial of regulatory approval of a product candidate. We may make formulation or manufacturing changes to our product candidates, in which case we may need to conduct additional preclinical studies to bridge our modified product candidates to earlier versions. If we experience delays in the commencement or completion of our clinical trials, or if we terminate a clinical trial prior to completion, the commercial prospects of our product candidates could be negatively impacted, and our ability to generate revenues from our product candidates may be delayed or eliminated entirely.

If we experience delays or difficulties in enrolling patients in our ongoing or planned clinical trials, our receipt of necessary regulatory approvals could be delayed or prevented.

We may not be able to initiate or continue our ongoing or planned clinical trials for our product candidates if we are unable to identify and enroll a sufficient number of eligible patients to participate in these trials as required by the FDA or comparable foreign regulatory authorities. In our tovorafenib (DAY101) program, we utilize genomic profiling of patients' tumors to identify suitable patients for recruitment into our clinical trials. We cannot be certain (i) how many patients will have the requisite alterations for inclusion in our clinical trials, (ii) that the number of patients enrolled in each program will suffice for regulatory approval or (iii) whether each specific BRAF mutation targeted will be included in the approved drug labeling. If our strategies for patient identification and enrollment prove unsuccessful, we may have difficulty enrolling or maintaining patients appropriate for our product candidates. The conditions for which we currently plan to evaluate our product candidates are orphan or rare diseases with limited patient pools from which to draw for clinical trials. The eligibility criteria of our clinical trials, once established, will further limit the pool of available trial participants. In addition, some of our competitors currently have ongoing clinical trials for product candidates that would treat the same patients as our clinical product candidates, and patients who would otherwise be eligible for our clinical trials may instead enroll in clinical trials of our competitors' product candidates. Further, if any of our competitors receive FDA approval for a product, it may limit our ability to enroll patients in our clinical trials if they decide to seek treatment with an approved product. For example, Novartis recently received approval for dabrafenib in combination with trametinib, which could in the future limit our ability to enroll patients in clinical trials for tovorafenib (DAY101). Patient enrollment is also affected by other factors, including:

- severity of the disease under investigation;
- our ability to recruit clinical trial investigators of appropriate competencies and experience;
- the incidence and prevalence of our target indications;
- clinicians' and patients' awareness of, and perceptions as to, the potential advantages and risks of our product candidates in relation to other available therapies, including any new drugs that may be approved for the indications we are investigating;
- the availability, expertise, and selection of contract research organizations, or CROs, to manage operations related to clinical trial enrollment;
- competing studies or trials with similar eligibility criteria;
- invasive procedures required to enroll patients and to obtain evidence of the product candidate's performance during the clinical trial;
- availability and efficacy of approved medications for the disease under investigation;

- eligibility criteria defined in the protocol for the trial in question;
- the size and nature of the patient population required for analysis of the trial's primary endpoints;
- efforts to facilitate timely enrollment in clinical trials;
- whether we are subject to a partial or full clinical hold on any of our clinical trials;
- reluctance of physicians or patient advocacy organizations to encourage patient participation in clinical trials;
- the ability to monitor patients adequately during and after treatment;
- our ability to obtain and maintain patient consents; and
- proximity and availability of clinical trial sites for prospective patients.

Our inability to enroll and maintain a sufficient number of patients for our clinical trials would result in significant delays or may require us to abandon one or more clinical trials altogether. There may be competing trials, as well as the limited bandwidth of pediatric oncology institutions for running trials, which can lead to the prioritization of certain trials, resulting in delays in our clinical trials. In addition, parents may be reluctant to enroll their children in our clinical trials, or may decide to withdraw their children from our clinical trials to pursue other therapies.

We face substantial competition which may result in others discovering, developing or commercializing products before or more successfully than we do.

The pharmaceutical and biotechnology industries are characterized by rapidly advancing technologies, intense competition and a strong emphasis on proprietary and novel products and product candidates. Our competitors have developed, are developing or may develop products, product candidates and processes competitive with our product candidates. Any product candidates that we successfully develop and commercialize will compete with existing therapies and new therapies that may become available in the future. We believe that a significant number of product candidates are currently under development, and may become commercially available in the future, for the treatment of conditions for which we may attempt to develop product candidates. In addition, our product candidates may need to compete with drugs physicians use off-label to treat the indications for which we seek approval. This may make it difficult for us to replace existing therapies with our product candidates.

In particular, there is intense competition in the field of oncology. We have competitors both in the United States and internationally, including major multinational pharmaceutical companies, established biotechnology companies, specialty pharmaceutical companies, emerging and start-up companies, universities and other research institutions.

We also compete with these organizations to recruit and retain qualified scientific, management and sales and marketing personnel, which could negatively affect our level of expertise and our ability to execute our business plan. We will also face competition in establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs.

We expect to face competition from existing products and products in development for each of our programs. Drug discovery efforts focused on V600 mutations have led to clinical success in some cancers. Three BRAF inhibitors have been approved by the FDA for the treatment of tumors containing V600E or V600K mutations. These first-generation BRAF inhibitors, known more generally as Type I RAF inhibitors, are vemurafenib, marketed as Zelboraf® by Genentech; dabrafenib, marketed as Tafinlar® by Novartis; and encorafenib, marketed as Braftovi® by Pfizer. Dabrafinib, in combination with trametinib, marketed as Mekinist® by Novartis, has been approved for the treatment of adult and pediatric patients ≥ 6 years of age with unresectable or metastatic solid tumors with BRAF V600E mutation who have progressed following prior treatment and have no satisfactory alternative treatment options. This includes BRAF V600E pLGG, a subset (10%-20%) of the greater RAF-altered pLGG clinical scope of the tovorafenib (DAY101) development program. Further, dabrafenib, in combination with trametinib, is being evaluated in a Novartis-sponsored randomized Phase 2 clinical trial in newly diagnosed patients with BRAF V600 mutant pLGG. Novartis has announced their plans to file a Supplemental New Drug Application based on data of this trial in early 2023.

Four MEK inhibitors have been approved by the FDA. Three have been approved for the treatment of tumors containing BRAF V600E or V600K mutations, including cobimetinib, marketed as Cotellic® by Genentech; trametinib, marketed as Mekinist® by Novartis; and binimetinib, marketed as Mektovi® by Pfizer. A fourth MEK inhibitor—selumetinib, marketed as Koselugo® by AstraZeneca—has been approved for the treatment of pediatric patients, two years of age and older, with neurofibromatosis type 1, or NF1, who have symptomatic, inoperable plexiform neurofibromas.

BeiGene has two next-generation BRAF programs: Lifirafenib (BGB-283), which is currently in a Phase 1/2 trial in combination with mirdametinib, and BGB-3245 which is currently in a single agent in Phase 1 dose escalation study. Hanmi/Genentech are developing belvarafenib in combination with cobimetinib in a Phase 1b clinical trial. Fore Therapeutics (formerly NovellusDx) is developing the RAF dimer breaker PLX8394 in a Phase 1/2 trial in combination with cobicistat. Kinnate is developing KIN-2787 in a monotherapy Phase 1 clinical trial as well as in combination with the MEK inhibitor binimetinib in a Phase 1b clinical trial. Black Diamond Therapeutics have next-generation BRAF inhibitors in various stages of preclinical development. Jazz Pharmaceuticals and Redx have announced that the pan-RAF inhibitor JZP815 has entered clinical development in a Phase 1 trial. Erasca recently announced that it has entered into an exclusive worldwide license agreement with Novartis for naporafenib, a Phase 2 pivotal-ready pan-RAF inhibitor with a potential first-in-class and best-in-class profile in NRAS mutant melanoma and other RAS/MAPK pathway-driven tumors.

With regard to the treatment of pLGG, some MEK inhibitors' and some type I RAF inhibitors' other targeted therapies are being studied in academic investigator-initiated clinical trials, and in some regions may be being used in an off-label manner. The off-label use of these agents may represent competition for tovorafenib (DAY101) when it enters the market.

Many of our competitors, either alone or with their collaborators, have significantly greater financial resources, established presence in the market, and expertise in research and development, manufacturing, preclinical and clinical testing, obtaining regulatory approvals and reimbursement and marketing approved products than we do.

Large pharmaceutical and biotechnology companies, in particular, have extensive experience in clinical testing, obtaining regulatory approvals, recruiting patients and manufacturing biotechnology product candidates. These companies also have significantly greater research, marketing and sales capabilities than we do and may also have product candidates that have been approved or are in late stages of development, and collaborative arrangements in our target markets with leading companies and research institutions. Established pharmaceutical and biotechnology companies may also invest heavily to accelerate discovery and development of novel compounds or to in-license novel compounds that could make the product candidates that we develop obsolete. Smaller or early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies, as well as in acquiring technologies complementary to, or necessary for, our programs.

As a result of all of these factors, our competitors may succeed in obtaining approval from the FDA or comparable foreign regulatory authorities or in discovering, developing and commercializing product candidates in our field before we do, which could result in our competitors establishing a strong market position before we are able to enter the market or could make our development more complicated.

Our potential 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, have a broader label, are marketed more effectively, are more widely reimbursed or are less expensive than any products that we may develop. Even if the product candidates we develop achieve marketing approval, they may be priced at a significant premium over competitive products if any have been approved by then, resulting in reduced competitiveness. Technological advances or products developed by our competitors may render our technologies or product candidates obsolete, less competitive or not economical. If we are unable to compete effectively, our opportunity to generate revenue from the sale of our products we may develop, if approved, could be adversely affected.

Adverse side effects, other safety risks or aesthetic side effects associated with tovorafenib (DAY101), pimasertib or any future product candidates we may develop could delay or preclude approval, cause us to suspend or discontinue clinical trials or abandon further development, limit the commercial profile of an approved product, or result in significant negative consequences following marketing approval, if any.

As is the case with pharmaceuticals generally, we have observed side effects and adverse events associated with our lead product candidate, tovorafenib (DAY101), and our other product candidates. These side effects included maculopapular rash, anemia, headache, elevation in blood creatinine phosphokinase (CPK), nausea, skin and hair discoloration and fatigue.

Results of our ongoing and planned clinical trials could reveal a high and unacceptable severity and prevalence of side effects or unexpected characteristics. Undesirable side effects caused by our product candidates could result in the delay, suspension or termination of clinical trials by us or regulatory authorities for a number of reasons. Furthermore, clinical trials by their nature utilize a sample of the potential patient population. With a limited number of subjects and limited duration of exposure, rare and severe side effects of our product candidates or those of our competitors may only be uncovered with a significantly larger number of patients exposed to the drug.

Additionally, patients treated with our product candidates have undergone, or may also be undergoing, medical, surgical, radiation and chemotherapy treatments, which can cause side effects or adverse events that are unrelated to our product candidates but may still impact the success of our clinical trials. 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 due to the gravity of such patients' illnesses. For example, it is expected that some of the patients to be enrolled in our future clinical trials will die or experience major clinical events either during the course of our clinical trials or after participating in such trials for non-treatment related reasons, which could impact development of tovorafenib (DAY101), pimasertib or our other product candidates. If we elect or are required to delay, suspend or terminate any clinical trial, the commercial prospects of our product candidates will be harmed and our ability to generate product revenues from such product candidate will be delayed or eliminated. Serious adverse events, or SAEs, observed in clinical trials could hinder or prevent market acceptance of our product candidates or reduce the duration of time that physicians expect to use our product in particular patients. Any of these occurrences may significantly harm our business, prospects, financial condition and results of operations.

Moreover, if our product candidates are associated with undesirable side effects in clinical trials or have characteristics that are unexpected, we may elect to abandon or limit their development to more narrow uses or subpopulations in which the undesirable side effects or other characteristics are less prevalent, less severe or more acceptable from a risk-benefit perspective, which may limit the commercial expectations for our product candidates, if approved. We may also be required to modify our study plans based on findings in our clinical trials. Such side effects could also affect patient recruitment or the ability of enrolled patients to complete the trial. Many drugs that initially showed promise in early-stage testing have later been found to cause side effects that prevented further development. In addition, regulatory authorities may draw different conclusions, require additional testing to confirm these determinations, require more restrictive labeling, or deny regulatory approval of the product candidate.

It is possible that, as we test our product candidates in larger, longer and more extensive clinical trials, including with different dosing regimens, or as the use of our product candidates becomes more widespread following any regulatory approval, illnesses, injuries, discomforts and other adverse events that were observed in earlier trials, as well as conditions that did not occur or went undetected in previous trials, will be reported by patients. If such side effects become known later in development or upon approval, if any, such findings may significantly harm our business, financial condition, results of operations and prospects significantly.

In addition, if any of our product candidates receive marketing approval, and we or others later identify undesirable side effects caused by treatment with such drug, a number of potentially significant negative consequences could result, including:

- regulatory authorities may withdraw approval of the drug;
- we may be required to recall a product or change the way the drug is administered to patients;
- regulatory authorities may require additional warnings in the labeling, such as a contraindication or a boxed warning, or issue safety alerts, Dear Healthcare Provider letters, press releases or other communications containing warnings or other safety information about the product

- we may be required to implement a REMS or create a medication guide outlining the risks of such side effects for distribution to patients;
- additional restrictions may be imposed on the marketing or promotion of the particular product or the manufacturing processes for the product or any component thereof;
- we could be sued and held liable for harm caused to patients;
- we may be subject to regulatory investigations and government enforcement actions;
- the drug could become less competitive; and
- our reputation may suffer.

Any of these events could prevent us from achieving or maintaining market acceptance of our product candidates, if approved, and could significantly harm our business, financial condition, results of operations and prospects.

Preliminary, interim, initial and topline data from our clinical trials that we announce or publish from time to time may change as more patient data become available and are subject to audit and verification procedures that could result in material changes in the final data.

From time to time, we may publicly disclose preliminary, interim or topline data from our clinical trials, such as the initial interim data and the topline data analysis for the pivotal Phase 2 of our tovorafenib (DAY101) trial. These updates are based on a preliminary analysis of then-available data, and the results and related findings and conclusions are subject to change following a more comprehensive review of the data related to the particular study or trial. Additionally, 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. Therefore, positive interim or initial results in any ongoing clinical trial may not be predictive of such results in the completed 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 initial or topline 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. Initial or topline 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.

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 and our company in general. 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 is the 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 drug, drug candidate or our business. If the topline data that we report differ from actual results, or if others, including regulatory authorities, disagree with the conclusions reached, our ability to obtain approval for, and commercialize, our product candidates may be harmed, which could harm our business, operating results, prospects or financial condition.

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.

Because we have limited financial and managerial resources, we focus on research programs and product candidates that we identify for specific indications. As a result, we may forego or delay pursuit of opportunities with other product candidates or for other indications that later prove to have greater commercial potential. 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 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.

The market opportunities for any product candidates we develop, if approved, may be limited to certain smaller patient subsets and may be smaller than we estimate them to be.

We plan to seek approval of tovorafenib (DAY101) as a treatment of both naïve and relapsed/progressive pLGG. There is no guarantee that our product candidates would be approved for either line of treatment, and prior to any such approvals we may have to conduct additional clinical trials that may be costly, time-consuming and subject to risk.

Our projections of both the number of people who have the cancers we are targeting, as well as the subset of people with these cancers in a position to receive a particular line of therapy and who have the potential to benefit from treatment with our product candidates, are based on our beliefs and estimates. For example, pLGG is a rare disease, and as such, our projections of both the number of people who have this disease, as well as the subset of people with pLGG who have the potential to benefit from treatment with our product candidates, are based on estimates. These estimates have been derived from a variety of sources, including scientific literature, surveys of clinics, patient foundations or market research, and may prove to be incorrect. Further, new studies may change the estimated incidence or prevalence of the cancers that we are targeting. The potentially addressable patient population for our product candidates may be limited or may not be amenable to treatment with our product candidates. Consequently, even if our product candidates are approved, the number of patients that may be eligible for treatment with our product candidates may turn out to be much lower than expected. In addition, we have not yet conducted market research to determine how treating physicians would expect to prescribe a product that is approved for multiple tumor types if there are different lines of approved therapies for each such tumor type. Even if we obtain significant market share for our products, if approved, if the potential target populations are small, we may never achieve profitability without obtaining regulatory approval for additional indications.

Our clinical development activities are primarily focused on the development of targeted therapeutics for patients with genomically defined cancers, which is a rapidly evolving area of science, and the approach we are taking to discover and develop drugs is novel and may never lead to approved or marketable products.

The discovery and development of targeted therapeutics for patients with genomically defined cancers is an emerging field, and the scientific discoveries that form the basis for our efforts to discover, identify and develop product candidates are relatively new. The scientific evidence to support the feasibility of developing product candidates based on these discoveries is both preliminary and limited. Although we believe, based on our product candidates' preclinical trial results and our clinical work, that the genomic alterations targeted by our programs are oncogenic drivers, clinical results may not confirm this hypothesis or may only confirm it for certain alterations or certain tumor types. The patient populations for our product candidates are limited to those with specific target alterations and may not be completely defined but are substantially smaller than the general treated cancer population, and we will need to screen and identify these patients with targeted alterations. Successful identification of patients is dependent on several factors, including achieving certainty as to how specific alterations respond to our product candidates and the ability to identify such alterations. Furthermore, even if we are successful in identifying patients, we cannot be certain that the resulting patient populations for each mutation will be large enough to allow us to successfully obtain approval for each mutation type and commercialize our product candidates and achieve profitability. In addition, even if our approach is successful in showing clinical benefit for RAF-driven cancers for our tovorafenib (DAY101) program, we may never successfully identify additional oncogenic alterations sensitive to tovorafenib (DAY101) in other MAPK-driven tumors. Therefore, we do not know if our approach of treating patients with genomically defined cancers will be successful, and if our approach is unsuccessful, our business will suffer.

Our product candidates may not achieve adequate market acceptance among physicians, patients or their families, healthcare payors and others in the medical community necessary for commercial success.

Even if our product candidates receive regulatory approval, they may not gain adequate market acceptance among physicians, patients or their families, third-party payors and others in the medical community. The degree of market acceptance of any of our approved product candidates will depend on a number of factors, including:

- the efficacy, durability and safety profile as demonstrated in clinical trials compared to alternative treatments, in addition to functional, quality, or patient-reported outcomes;
- the timing of market introduction of the product candidate as well as competitive products;
- the clinical indications for which a product candidate is approved;
- restrictions on the use of product candidates in the labeling approved by regulatory authorities, such as boxed warnings or contraindications in labeling, or a REMS, if any, which may not be required of alternative treatments and competitor products;
- the potential and perceived advantages of our product candidates over alternative treatments;
- the cost of treatment in relation to alternative treatments and the cost/benefit ratios of each;
- the availability of coverage and adequate reimbursement by third-party payors, including government authorities, and timing of relevant formulary decision-making resulting in this coverage and reimbursement;
- the availability of an approved product candidate for use as a combination therapy;
- relative convenience and ease of administration in relation to competition;
- the willingness of the target patient population (which may include willingness of our pediatric patients' parents) to try new therapies and undergo required diagnostic screening to determine treatment eligibility and of physicians to prescribe these therapies and diagnostic tests;
- the effectiveness of sales, marketing efforts and market access;
- unfavorable publicity relating to our product candidates; and
- the approval of other new therapies for the same indications.

If any of our product candidates are approved but do not achieve an adequate level of acceptance by physicians, hospitals, healthcare payors and patients, we may not generate or derive sufficient revenue from that product candidate and our financial results could be negatively impacted.

Any product candidates we develop may become subject to unfavorable third-party coverage and reimbursement practices, as well as pricing regulations.

The availability and extent of coverage and adequate reimbursement by third-party payors, including government health administration authorities, private health coverage insurers, managed care organizations and other third-party payors is essential for most patients to be able to afford expensive treatments. Sales of any of our product candidates that receive marketing approval will depend substantially, both in the United States and internationally, on the extent to which the costs of such product candidates will be covered and reimbursed by third-party payors. If reimbursement is not available, or is available only to limited levels, we may not be able to successfully commercialize our product candidates. Even if coverage is provided, the approved reimbursement amount may not be high enough to allow us to establish or maintain pricing sufficient to realize an adequate return on our investment. Coverage and reimbursement may impact the demand for, or the price of, any product candidate for which we obtain marketing approval. If coverage and reimbursement are not available or reimbursement is available only to limited levels, we may not successfully commercialize any product candidate for which we obtain marketing approval.

There is significant uncertainty related to third-party payor coverage and reimbursement of newly approved products. The payor mix for pediatric products in the United States is a fragmented combination of state-specific Medicaid policies and a broad universe of private insurance companies. There is no consistent policy or leading payor to inform other price-setting entities. National payor policies are expected to be critical to our ability to achieve broad payment coverage. However, one third-party payor's determination to provide coverage for a product candidate does not assure that other payors will also provide coverage for the product candidate. As a result, the coverage determination process is often time-consuming and costly. This process will require us to provide scientific and clinical support for the use of our products to each third-party payor separately, with no assurance that coverage and adequate reimbursement will be applied consistently or obtained in the first instance.

As federal and state governments implement additional health care cost containment measures, including measures to lower prescription drug pricing, we cannot be sure that our products, if approved, will be covered by private or public payors, and if covered, whether the reimbursement will be adequate or competitive with other marketed products. These and other actions by federal and state governments and health plans may put additional downward pressure on pharmaceutical pricing and health care costs, which could negatively impact coverage and reimbursement for our products if approved, our revenue, and our ability to compete with other marketed products and to recoup the costs of our research and development.

Increasingly, third-party payors are requiring that drug companies provide them with predetermined discounts from list prices and are challenging the prices charged for medical products. Further, such payors are increasingly challenging the price, examining the medical necessity and reviewing the cost effectiveness of medical product candidates. There may be especially significant delays in obtaining coverage and reimbursement for newly approved drugs. Third-party payors may limit coverage to specific product candidates on an approved list, known as a formulary, which might not include all FDA-approved drugs for a particular indication. We plan to conduct expensive pharmaco-economic studies to demonstrate the medical necessity and cost-effectiveness of our products. Nonetheless, our product candidates may not be considered medically necessary or cost-effective. We cannot be sure that coverage and reimbursement will be available for any product that we commercialize and, if reimbursement is available, what the level of reimbursement will be.

In addition, companion diagnostic tests require coverage and reimbursement separate and apart from the coverage and reimbursement for their companion pharmaceutical or biological products. Similar challenges to obtaining coverage and reimbursement, applicable to pharmaceutical or biological products, will apply to companion diagnostics. Additionally, if any companion diagnostic provider is unable to obtain reimbursement or is inadequately reimbursed, that may limit the availability of such companion diagnostic, which would negatively impact prescriptions for our product candidates, if approved.

Outside the United States, the commercialization of therapeutics is generally subject to extensive governmental price controls and other market regulations, and we believe the increasing emphasis on cost containment initiatives in Europe, Canada and other countries has and will continue to put pressure on the pricing and usage of therapeutics such as our product candidates. In many countries, particularly the countries of the European Union, or EU, medical product prices are subject to varying price control mechanisms as part of national health systems. In these countries, pricing negotiations with governmental authorities can take considerable time after a product receives marketing approval. To obtain 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. In general, product prices under such systems are substantially lower than in the United States. Other countries allow companies to fix their own prices for products but monitor and control company profits. Additional foreign price controls or other changes in pricing regulation could restrict the amount that we are able to charge for our product candidates. Accordingly, in markets outside the United States, the reimbursement for our products may be reduced compared with the United States and may be insufficient to generate commercially reasonable revenue and profits.

If we are unable to establish or sustain coverage and adequate reimbursement for any product candidates from third-party payors, the adoption of those products and sales revenue will be adversely affected, which, in turn, could adversely affect the ability to market or sell those product candidates, if approved. Coverage policies and third-party payor reimbursement rates may change at any time. 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.

Our business entails a significant risk of product liability and if we are unable to obtain sufficient insurance coverage such inability could have an adverse effect on our business and financial condition.

Our business exposes us to significant product liability risks inherent in the development, testing, manufacturing and marketing of therapeutic treatments. Product liability claims could delay or prevent completion of our development programs. If we succeed in marketing products, such claims could result in an FDA or other regulatory authority investigation of the safety and effectiveness of our products, our manufacturing processes and facilities or our marketing programs. FDA or other regulatory authority investigations could potentially lead to a recall of our products or more serious enforcement action, limitations on the approved indications for which they may be used or suspension or withdrawal of approvals. Regardless of the merits or eventual outcome, liability claims may also result in decreased demand for our products, injury to our reputation, costs to defend the related litigation, a

diversion of management's time and our resources and substantial monetary awards to trial participants or patients. We currently have product liability insurance that we believe is appropriate for our stage of development and may need to obtain higher levels prior to advancing our product candidates into clinical trials or marketing any of our product candidates, if approved. Any insurance we have or may obtain may not provide sufficient coverage against potential liabilities. Furthermore, clinical trial and product liability insurance is becoming increasingly expensive. As a result, we may be unable to obtain sufficient insurance at a reasonable cost to protect us against losses caused by product liability claims that could have an adverse effect on our business and financial condition.

Risks related to Government Regulation

The development and commercialization of pharmaceutical products are subject to extensive regulation, and we may not obtain regulatory approvals for tovorafenib (DAY101), pimasertib or any future product candidates, on a timely basis or at all.

The clinical development, manufacturing, labeling, packaging, storage, recordkeeping, advertising, promotion, export, import, marketing, distribution, adverse event reporting, including the submission of safety and other post-marketing information and reports, and other possible activities relating to tovorafenib (DAY101) and pimasertib, currently our only product candidates in planned or ongoing clinical trials, as well as any other product candidate that we may develop in the future, are subject to extensive regulation. Marketing approval of drugs in the United States requires the submission of an NDA to the FDA, and we are not permitted to market any product candidate in the United States until we obtain approval from the FDA of the NDA for that product. An NDA must be supported by extensive clinical and preclinical data, as well as extensive information regarding pharmacology, chemistry, manufacturing and controls. Our product candidates must be approved by comparable regulatory authorities in other jurisdictions prior to commercialization.

FDA approval of an NDA is not guaranteed, and the review and approval process is an expensive and uncertain process that may take several years. Of the large number of drugs in development in the United States, only a small percentage will successfully complete the FDA regulatory approval process and will be commercialized. Accordingly, there can be no assurance that any of our product candidates will receive regulatory approval in the United States, or other jurisdictions.

The FDA also has substantial discretion in the approval process. The number and types of preclinical studies and clinical trials that will be required for NDA approval varies depending on the product candidate, the disease or the condition that the product candidate is designed to treat and the regulations applicable to any particular product candidate. For example, if successful, we believe that the pivotal Phase 2 FIREFLY-1 trial of tovorafenib (DAY101) may be sufficient to support FDA approval of an NDA for tovorafenib (DAY101), but the FDA may disagree with the sufficiency of our data and require additional clinical trials. Additionally, depending upon the results of the pivotal Phase 2 FIREFLY-1 trial of tovorafenib (DAY101), we may receive accelerated approval for tovorafenib (DAY101), which would require additional data and potentially a confirmatory trial to validate the clinical benefit of the drug. Despite the time and expense associated with preclinical studies and clinical trials, failure can occur at any stage. The results of preclinical and early clinical trials of tovorafenib (DAY101) or pimasertib or any other product candidate may not be predictive of the results of our later-stage clinical trials. Additionally, we have become aware of competitor clinical trials in front-line pLGG and we believe the FDA and other regulators may consider the design and results of these trials when evaluating our front-line program. For example, while we may believe certain results in patients, such as stable disease, suggest encouraging clinical activity, stable disease is not considered a response for regulatory purposes in an endpoint assessing overall response rate, or ORR.

In addition, we may experience delays or rejections based upon additional government regulation from future legislation or administrative action, or changes in regulatory authority policy during the period of product development, clinical trials, and the review process. For example, in May 2022, the Oncology Center of Excellence within the FDA has recently advanced Project Optimus, which is an initiative to reform the dose optimization and dose selection paradigm in oncology drug development to emphasize selection of an optimal dose, which is a dose or doses that maximizes not only the efficacy of a drug but the safety and tolerability as well. This shift from the prior approach, which generally determined the maximum tolerated dose, may require sponsors to spend additional time and resources to further explore a product candidate's dose-response relationship to facilitate optimum dose selection in a target population. Other recent Oncology Center of Excellence initiatives have included Project FrontRunner, a new initiative with a goal of developing a framework for identifying candidate drugs for initial

clinical development in the earlier advanced setting rather than for treatment of patients who have received numerous prior lines of therapies or have exhausted available treatment options.

Clinical trial failure may result from a multitude of factors including flaws in trial design, dose selection, placebo effect, patient enrollment criteria and failure to demonstrate favorable safety or efficacy traits, and failure in clinical trials can occur at any stage. Companies in the pharmaceutical industry frequently suffer setbacks in the advancement of clinical trials due to lack of efficacy or adverse safety profiles, notwithstanding promising results in earlier trials. Based upon negative or inconclusive results, we may decide, or regulators may require us, to conduct additional clinical trials or preclinical studies. In addition, data obtained from clinical trials are susceptible to varying interpretations, and regulators may not interpret our data as favorably as we do, which may further delay, limit or prevent marketing approval. The FDA could delay, limit or deny approval of a product candidate for many reasons, including because the FDA may:

- not deem our product candidate to be safe and effective;
- determine that the product candidate does not have an acceptable benefit-risk profile;
- determine in the case of an NDA seeking accelerated approval that the NDA does not provide evidence that the product candidate represents a meaningful advantage over available therapies;
- determine that ORR as the primary endpoint, complemented by key secondary endpoints, is insufficient to reliably define clinical benefit;
- not agree that the data collected from preclinical studies and clinical trials are acceptable or sufficient to support the submission of an NDA or other submission or to obtain regulatory approval, and may impose requirements for additional preclinical studies or clinical trials;
- determine that adverse events experienced by participants in our clinical trials represent an unacceptable level of risk;
- determine that 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;
- 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;
- disagree regarding the formulation, labeling and/or the specifications;
- not approve the manufacturing processes associated with our product candidate or may determine that a manufacturing facility does not have an acceptable compliance status;
- change approval policies or adopt new regulations; or
- not file a submission due to, among other reasons, the content or formatting of the submission.

We have not obtained FDA approval for any product. This lack of experience may impede our ability to obtain FDA approval in a timely manner, if at all, for our clinical product candidates. Furthermore, even if we receive FDA approval, there is no assurance that we will receive similar approval from comparable regulatory authorities in foreign jurisdictions, which may limit our addressable market and could adversely affect our business, prospects, financial condition and results of operations.

If we experience delays in obtaining approval or if we fail to obtain approval of tovorafenib (DAY101) or pimasertib, or our future product candidates, if any, our commercial prospects will be harmed and our ability to generate revenues will be materially impaired, which would adversely affect our business, prospects, financial condition and results of operations.

The accelerated approval pathway for our product candidates may not lead to a faster development or regulatory review or approval process and does not increase the likelihood that our product candidates will receive marketing approval.

Under the FDA's accelerated approval program, the FDA may approve a drug for a serious or life-threatening illness that provides meaningful therapeutic benefit to patients over existing treatments based upon 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, 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. We may seek accelerated approval for one or more of our product candidates on the basis of ORR, a surrogate endpoint that we believe is reasonably likely to predict clinical benefit.

For drugs granted accelerated approval, post-marketing confirmatory trials are required to describe the anticipated effect on irreversible morbidity or mortality or other clinical benefit. These confirmatory trials must be completed with due diligence and, in most cases, the FDA may require that the trial be designed, initiated, and/or fully enrolled prior to approval. If any of our competitors were to receive full approval for an indication for which we are seeking accelerated approval before we receive accelerated approval, the indication we are seeking may no longer qualify as a condition for which there is an unmet medical need and accelerated approval of our product candidate would be more difficult or may not occur. Moreover, the FDA may withdraw approval of our product candidate approved under the accelerated approval pathway if, for example:

- the trial or trials required to verify the predicted clinical benefit of our product candidate fail to verify such benefit or do not demonstrate sufficient clinical benefit to justify the risks associated with the drug;
- other evidence demonstrates that our product candidate is not shown to be safe or effective under the conditions of use;
- we fail to conduct any required post-approval trial of our product candidate with due diligence; or
- we disseminate false or misleading promotional materials relating to the relevant product candidate.

Recently, the accelerated approval pathway has come under scrutiny within the FDA and by Congress. The FDA has put increased focus on ensuring that confirmatory studies are conducted with diligence and, ultimately, that such studies confirm the benefit. For example, the FDA has convened its Oncologic Drugs Advisory Committee to review what the FDA has called dangling or delinquent accelerated approvals where confirmatory studies have not been completed or where results did not confirm benefit. In addition, in 2021, the Oncology Center of Excellence announced Project Confirm, which is an initiative to promote the transparency of outcomes related to accelerated approvals for oncology indications and provide a framework to foster discussion, research and innovation in approval and post-marketing processes, with the goal to enhance the balance of access and verification of benefit for therapies available to patients with cancer and hematologic malignancies. Furthermore, in addition, Congress is considering various proposals to potentially make changes to the accelerated approval pathway, including proposals to increase the likelihood of withdrawal of approval in such circumstances.

Even though we have received breakthrough therapy designation by the FDA for tovorafenib (DAY101) in treating pLGG, such designation may not lead to a faster development or regulatory review or approval process, and it does not increase the likelihood that tovorafenib (DAY101) will receive marketing approval.

We have received breakthrough therapy designation by the FDA for tovorafenib (DAY101) in patients with advanced pLGG. A breakthrough therapy is defined as a drug that is intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition, and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. For drugs that have been designated as breakthrough therapies, interaction and communication between the FDA and the sponsor of the trial can help to identify the most efficient path for clinical development while minimizing the number of patients placed in ineffective control regimens. Drugs designated as breakthrough therapies by the FDA are also eligible for priority review if supported by clinical data at the time of the submission of the NDA.

Although breakthrough therapy designation or access to any other expedited program may expedite the development or approval process, it does not change the standards for approval. Although we obtained Breakthrough Therapy designation for tovorafenib (DAY101) in advanced pLGG, we may not experience faster development timelines or achieve faster review or approval compared to conventional FDA procedures. For example, the time required to identify and resolve issues relating to manufacturing and controls, the acquisition of a sufficient supply of our product for clinical trial purposes or the need to conduct additional nonclinical or clinical studies may delay approval by the FDA, even if the product qualifies for Breakthrough Therapy designation or access to any other expedited program. Access to an expedited program may also be withdrawn by the FDA if it believes that the designation is no longer supported by data from our clinical development program. Additionally, qualification for any expedited review procedure does not ensure that we will ultimately obtain regulatory approval for such product.

We may not be able to obtain or maintain orphan drug designation or exclusivity for our product candidates.

We have obtained orphan drug designation in the United States and in the EU for use of tovorafenib (DAY101) in treating malignant glioma and glioma, respectively. We may seek orphan drug designation for tovorafenib (DAY101) in additional geographies or indications, or for pimasertib or any product candidates we develop in the future. Regulatory authorities in some jurisdictions, including the United States, may designate drugs for relatively small patient populations as "orphan drugs." Under the Orphan Drug Act, the FDA may designate a drug as an orphan drug if it is intended to treat a rare disease or condition, which is generally defined as a patient population of fewer than 200,000 individuals in the United States, or if the disease or condition affects more than 200,000 individuals in the United States and there is no reasonable expectation that the cost of developing the drug for the type of disease or condition will be recovered from sales of the product in the United States.

Generally, if a product with an orphan drug designation subsequently receives the first marketing approval for the indication for which it has such designation, the product is entitled to a period of marketing exclusivity, which precludes the FDA from approving another marketing application for the same drug for the same indication during that time period. The applicable period is seven years in the United States and ten years in the EU. The EU exclusivity period can be reduced to six years if a drug no longer meets the criteria for orphan drug designation or if the drug is sufficiently profitable so that market exclusivity is no longer justified. Orphan drug exclusivity in the United States may be lost if the FDA determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantity of the drug to meet the needs of patients with the rare disease or condition.

The FDA may approve a subsequent application to market the same drug for the same indication during the exclusivity period in certain circumstances, such as if the subsequent product demonstrates clinical superiority (i.e., the subsequent product is safer, more effective or makes a major contribution to patient care) over the product with orphan exclusivity. Competitors, however, may receive approval of different products for the same indication for which the orphan product has exclusivity, or obtain approval for the same product but for a different indication than that for which the orphan product has exclusivity. Orphan drug designation also entitles a party to financial incentives, such as opportunities for grant funding towards clinical trial costs, tax advantages and user-fee waivers.

We cannot assure you that any future application for orphan drug designation with respect to any other product candidate will be granted. If we are unable to obtain orphan drug designation with respect to other product candidates in the United States or other jurisdictions, we will not be eligible to obtain the period of market exclusivity that could result from orphan drug designation or be afforded the financial incentives associated with orphan drug designation.

Moreover, a recent Eleventh Circuit decision in Catalyst Pharmaceuticals, Inc. vs. FDA regarding interpretation of the Orphan Drug Act exclusivity provisions as applied to drugs approved for orphan indications narrower than the drug's orphan designation has the potential to significantly broaden the scope of orphan drug exclusivity for such products. Depending on how broadly the FDA applies the Catalyst decision, it could fundamentally change how companies rely on, or seek to work around, orphan drug exclusivity. Legislation has also been introduced that may reverse the Catalyst decision, but such legislation is still in early stages and has not been passed.

We may seek a rare pediatric disease designation for one or more of our product candidates. Even if we were to obtain approval for our product candidates with the rare pediatric disease designation, the Rare Pediatric Disease Priority Review Voucher program may no longer be in effect at the time of such approval or we might not be able to capture the value of the Rare Pediatric Disease Priority Review Voucher program.

Tovorafenib (DAY101) was granted rare pediatric designation by the FDA in May 2021 for tovorafenib (DAY101) in the treatment of low-grade gliomas, or LGGs, harboring an activating RAF alteration that disproportionately affects children. We intend to submit the initial tovorafenib (DAY101) NDA as a rare pediatric designation marketing application which may or may not be designated as such by the FDA upon review.

Congress authorized the FDA to award priority review vouchers to sponsors of certain rare pediatric disease product applications that meet the specified criteria. These vouchers are designed to encourage development of new drug and biological products for prevention and treatment of certain rare pediatric diseases.

Specifically, under this program, a sponsor who receives an approval for a drug or biologic for a "rare pediatric disease" may qualify for a voucher that can be redeemed to receive a priority review of a subsequent marketing application for a different product. The sponsor of a rare pediatric disease drug product receiving a priority review voucher may transfer (including by sale) the voucher to another sponsor. The voucher may be further transferred any number of times before the voucher is used, as long as the sponsor making the transfer has not yet submitted the application. Although the voucher can be sold or transferred to third parties, there is no guarantee that we will be able to receive such voucher, or realize any value if we receive and were to sell the voucher.

For the purposes of this program, a rare pediatric disease is a (i) serious or life-threatening disease in which the serious or life-threatening manifestations primarily affect individuals aged from birth to 18 years, including age groups often called neonates, infants, children, and adolescents; and (ii) rare disease or condition within the meaning of the Orphan Drug Act. The FDA may determine that an application for one or more of our product candidates does not meet the eligibility criteria for a priority review voucher upon approval.

Moreover, while the opportunity to receive a priority review voucher was meant to expire for those companies that had not received a designation by September 30, 2020, the Rare Pediatric Disease Priority Review Voucher program was extended by Congress in December 2020. Under the current statutory sunset provisions, after September 30, 2024, the FDA may only award a voucher for an approved rare pediatric disease product application if the sponsor has rare pediatric disease designation for the drug, and that designation was granted by September 30, 2024. After September 30, 2026, the FDA may not award any rare pediatric disease priority review vouchers.

If we decide to pursue a Fast Track Designation by the FDA, it may not lead to a faster development or regulatory review or approval process.

We may seek Fast Track Designation for one or more of our product candidates. If a drug is intended for the treatment of a serious or life-threatening condition and the drug demonstrates the potential to address unmet medical needs for this condition, the product sponsor may apply for FDA Fast Track Designation. The FDA has broad discretion whether to grant this designation, so even if we believe a particular product candidate is eligible for this designation, we cannot assure you that the FDA would decide to grant it. Even if we do receive Fast Track Designation, we may not experience a faster development process, review or approval compared to conventional FDA procedures. The FDA may withdraw Fast Track Designation if it believes that the designation is no longer supported by data from our clinical development program.

If we are unable to successfully develop, validate, obtain regulatory approval of and commercialize companion diagnostic tests for any product candidates that require such tests, or experience significant delays in doing so, we may not realize the full commercial potential of these product candidates.

A companion diagnostic is a medical device, often an *in vitro* device, which provides information that is essential for the safe and effective use of a corresponding therapeutic drug product. A companion diagnostic can be used to identify patients who are most likely to benefit from the therapeutic product. In the future, if required to develop a companion diagnostic, we may evaluate opportunities to develop, either by ourselves or with collaborators, companion diagnostic tests for our product candidates for certain indications.

A companion diagnostic is generally developed in conjunction with the clinical program for an associated therapeutic product. To date, the FDA has required premarket approval of the vast majority of companion diagnostics for cancer therapies. Generally, when a companion diagnostic is essential to the safe and effective use of a drug product, the FDA requires that the companion diagnostic be approved before or concurrent with approval of the therapeutic product and before such product can be commercialized. The approval of a companion diagnostic as part of the therapeutic product's labeling limits the use of the therapeutic product to only those patients who express the specific genetic alteration that the companion diagnostic was developed to detect.

Development of a companion diagnostic could include additional meetings with regulatory authorities, such as a pre-submission meeting and the requirement to submit an investigational device exemption application. In the case of a companion diagnostic that is designated as "significant risk device," approval of an investigational device exemption by the FDA and IRB is required before such diagnostic is used in conjunction with the clinical trials for a corresponding product candidate.

To be successful in developing, validating, obtaining approval of and commercializing a companion diagnostic, we or our collaborators will need to address a number of scientific, technical, regulatory and logistical challenges. We have no prior experience with medical device or diagnostic test development. If we choose to develop and seek FDA approval for companion diagnostic tests on our own, we will require additional personnel. We may rely on third parties for the design, development, testing, validation and manufacture of companion diagnostic tests for our therapeutic product candidates that require such tests, the application for and receipt of any required regulatory approvals, and the commercial supply of these companion diagnostics. If these parties are unable to successfully develop companion diagnostics for these therapeutic product candidates, or experience delays in doing so, we may be unable to enroll enough patients for our current and planned clinical trials, the development of these therapeutic product candidates may be adversely affected, these therapeutic product candidates may not obtain marketing approval, and we may not realize the full commercial potential of any of these therapeutics that obtain marketing approval. For any product candidate for which a companion diagnostic is necessary to select patients who may benefit from use of the product candidate, any failure to successfully develop a companion diagnostic may cause or contribute to delayed enrollment of our clinical trials, and may prevent us from initiating a pivotal trial. In addition, the commercial success of any of our product candidates that require a companion diagnostic will be tied to and dependent upon the receipt of required regulatory approvals and the continued ability of such third parties to make the companion diagnostic commercially available to us on reasonable terms in the relevant geographies. There is no guarantee that physicians will adopt any particular companion diagnostic, be willing to understand how to use it, how to obtain reimbursement for it, how to explain it to patients, or dedicate staff to using it. Any failure to do so could materially harm our business, results of operations and financial condition.

Even if we obtain marketing approval for our product candidates, the terms of approvals, ongoing regulation of our products or other post-approval restrictions may limit how we manufacture and market our products and compliance with such requirements may involve substantial resources, which could materially impair our ability to generate revenue.

Any product candidates for which we receive accelerated approval from the FDA are required to undergo one or more confirmatory clinical trials. If such a product candidate fails to meet its safety and efficacy endpoints in such confirmatory clinical trials, the regulatory authority may withdraw its conditional approval. There is no assurance that any such product will successfully advance through its confirmatory clinical trial(s). Therefore, even if a product candidate receives accelerated approval from the FDA, such approval may be withdrawn at a later date. Even if marketing approval of a product candidate is granted, an approved product and its manufacturer and marketer, are subject to ongoing review and extensive regulation, which may include the requirement to implement a REMS or to conduct costly post-marketing studies or clinical trials and surveillance to monitor the safety or efficacy of the product.

We must also comply with requirements concerning advertising and promotion for any of our product candidates for which we obtain marketing approval. Promotional communications with respect to prescription drugs are subject to a variety of legal and regulatory restrictions and must be consistent with the information in the product's approved labeling. Thus, we will not be able to promote any products we develop for indications or uses for which they are not approved.

In addition, manufacturers of approved products and those manufacturers' facilities are required to ensure that quality control and manufacturing procedures conform to current good manufacturing practices, or cGMPs, which include requirements relating to quality control and quality assurance as well as the corresponding maintenance of records and documentation and reporting requirements. We and our CMOs could be subject to periodic unannounced inspections by the FDA to monitor and ensure compliance with cGMPs.

Accordingly, assuming we obtain marketing approval for one or more of our product candidates, we and our CMOs will continue to expend time, money and effort in all areas of regulatory compliance, including manufacturing, production, product surveillance and quality control. If we are not able to comply with post-approval regulatory requirements, we could have the marketing approvals for our products withdrawn by regulatory authorities and our ability to market any future products could be limited, which could adversely affect our ability to achieve or sustain profitability. As a result, the cost of compliance with post-approval regulations may have a negative effect on our operating results and financial condition.

Any product candidate for which we obtain marketing approval will be subject to ongoing enforcement of post-marketing requirements by regulatory agencies, and we could be subject to substantial penalties, including withdrawal of our product from the market, if we fail to comply with all regulatory requirements or if we experience unanticipated problems with our products, when and if any of them are approved.

Any product candidate for which we obtain marketing approval, along with the manufacturing processes, post-approval clinical data, labeling, advertising and promotional activities for such product, will be subject to continual requirements of and review by the FDA and other regulatory authorities. These requirements include, but are not limited to, restrictions governing promotion of an approved product, submissions of safety and other post-marketing information and reports, registration and listing requirements, cGMP requirements relating to manufacturing, quality control, quality assurance and corresponding maintenance of records and documents, and requirements regarding drug distribution and the distribution of samples to physicians and recordkeeping.

The FDA and other federal and state agencies, including the Department of Justice, closely regulate compliance with all requirements governing prescription drug products, including requirements pertaining to marketing and promotion of drugs in accordance with the provisions of the approved labeling and manufacturing of products in accordance with cGMP requirements. For example, the FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses, and a company that is found to have improperly promoted off-label uses may be subject to significant liability. Violations of such requirements may lead to investigations alleging violations of the Federal Food, Drug, and Cosmetic Act, or FDCA, 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 revenues;
- suspension or withdrawal of marketing approvals;
- 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.

Non-compliance by us or any future collaborator with regulatory requirements, including safety monitoring or pharmacovigilance, and with requirements related to the development of products for the pediatric population can also result in significant financial penalties.

Our failure to obtain marketing approval in foreign jurisdictions would prevent our product candidates from being marketed in those jurisdictions, and any approval we are granted for our product candidates in the United States would not assure approval of product candidates in foreign jurisdictions.

In order to market and sell our products in any jurisdiction outside the United States, we must obtain separate marketing approvals and comply with numerous and varying regulatory requirements. The approval procedure varies among countries and can involve additional testing. The time required to obtain approval may differ substantially from that required to obtain FDA approval. The regulatory approval process outside the United States generally includes all of the risks associated with obtaining FDA approval. In addition, in many countries outside the United States, it is required that the product be approved for reimbursement before the product can be approved for sale in that country. We may not obtain approvals from regulatory authorities outside the United States on a timely basis, if at all. Approval by the FDA does not ensure approval by regulatory authorities in other countries or jurisdictions, and approval by one regulatory authority outside the United States does not ensure approval by regulatory authorities in other countries or jurisdictions or by the FDA. We may not be able to submit for marketing approvals and may not receive necessary approvals to commercialize our products in any market.

Our current and future relationships with customers and third-party payors may be subject to applicable anti-kickback, fraud and abuse, transparency, health privacy, and other healthcare laws and regulations, which could expose us to significant penalties, including criminal, civil, and administrative penalties, contractual damages, reputational harm and diminished profits and future earnings.

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 current and future arrangements with healthcare providers, third-party payors and customers may expose us to broadly applicable fraud and abuse and other healthcare laws and regulations that may constrain the business or financial arrangements and relationships through which we research, as well as, market, sell and distribute any products for which we obtain marketing approval. Restrictions under applicable federal and state healthcare laws and regulations that may be applicable to our business include the following:

- the federal Anti-Kickback Statute prohibits, among other things, persons and entities from knowingly and willfully soliciting, offering, receiving or providing remuneration, directly or indirectly, in cash or in kind, to induce or reward, or in return for, either the referral of an individual for, or the purchase, order or recommendation of, any good or service, for which payment may be made under a federal healthcare program such as Medicare and Medicaid;
- the federal civil false claims laws, including the False Claims Act, which can be enforced by civil whistleblower or qui tam actions on behalf of the government, and criminal false claims laws and the civil monetary penalties law, prohibit individuals or entities from, among other things, knowingly presenting, or causing to be presented false or fraudulent claims for payment by a federal government program, or making a false statement or record material to payment of a false claim or avoiding, decreasing or concealing an obligation to pay money to the federal government;

- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, prohibits, among other things, knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program, regardless of the payor (e.g. public or private), and knowingly and willfully falsifying, concealing or covering up by any trick or device a material fact or making any materially false, fictitious or fraudulent statements in connection with the delivery of, or payment for, healthcare benefits, items or services relating to healthcare matters;
- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, or HITECH, and their implementing regulations, imposes requirements on certain covered healthcare providers, health plans, and healthcare clearinghouses as well as their respective business associates and their subcontractors that perform services for them that involve the use, or disclosure of, individually identifiable health information, relating to the privacy, security, and transmission of such individually identifiable health information;
- the federal transparency requirements under the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, collectively referred to as the ACA, require certain manufacturers of drugs, devices, biologics and medical supplies to annually report to the Centers for Medicare & Medicaid Services, or CMS, information related to payments and other transfers of value provided to teaching hospitals, as well as ownership and investment interests held by physicians, defined to include doctors, dentists, optometrists, podiatrists and chiropractors, and their immediate family members. Beginning January 1, 2021, manufacturers are required to collect information regarding payments and transfers of value to physician assistants, nurse practitioners, clinical nurse specialists, anesthesiologist assistants, certified nurse anesthetists and certified nurse-midwives for reporting in the following year. The reported information is made available on a public website; and
- analogous state laws and regulations such as state anti-kickback and false claims laws and analogous non-U.S. fraud and abuse laws and regulations, may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental third-party payors, including private insurers. Some state laws require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance regulations promulgated by the federal government and may require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers, marketing expenditures, or drug pricing, including price increases. Certain state and local laws require the registration of pharmaceutical sales representatives. Certain state and non-U.S. laws, many of which differ from each other in significant ways and often are not preempted by HIPAA, also govern the privacy and security of health information in some circumstances, thus complicating compliance efforts.

Efforts to ensure that our internal business processes and business arrangements with third parties will comply with applicable healthcare laws and regulations will involve substantial costs. It is possible that governmental authorities will conclude that our business practices may not comply with current or future statutes, regulations 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 these laws or any other governmental regulations that may apply to us, we may be subject to significant civil, criminal and administrative penalties, damages, fines, disgorgement, imprisonment, exclusion from government funded healthcare programs, such as Medicare and Medicaid and other federal healthcare programs, contractual damages, reputational harm, diminished profits and future earnings, additional integrity reporting and oversight obligations, and the curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and our results of operations. If any of the physicians or other healthcare providers or entities with whom we expect to do business is found to be not in compliance with applicable laws, they may be subject to significant criminal, civil and administrative sanctions, including exclusions from government funded healthcare programs, which could have a material adverse effect on our business, results of operations, financial condition and prospects.

Recently enacted and future legislation may increase the difficulty and cost for us to obtain marketing approval of and commercialize our product candidates and decrease the prices we may obtain.

In the United States and some foreign jurisdictions, there have been a number of legislative and regulatory changes and proposed changes regarding 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 candidates for which we obtain marketing approval.

For example, in March 2010, the ACA was signed into law. The ACA is a sweeping law intended to broaden access to health insurance, reduce or constrain the growth of healthcare spending, enhance remedies against fraud and abuse, add new transparency requirements for the healthcare and health insurance industries, impose new taxes and fees on the health industry and impose additional health policy reforms.

Among the provisions of the ACA of importance to our potential product candidates are the following:

- annual fees and taxes on manufacturers of certain branded prescription drugs;
- an annual, nondeductible fee on any entity that manufactures or imports specified branded prescription drugs and biologic products;
- a Medicare Part D coverage gap discount program, in which manufacturers must now agree to offer 70% 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;
- a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted or injected;
- an increase in the statutory minimum rebates a manufacturer must pay under the Medicaid Drug Rebate Program and extended the rebate program to individuals enrolled in Medicaid managed care organizations;
- expansion of healthcare fraud and abuse laws, including the False Claims Act and the federal Anti-Kickback Statute, new government investigative powers, and enhanced penalties for noncompliance;
- extension of manufacturers' Medicaid rebate liability;
- expansion of eligibility criteria for Medicaid programs;
- expansion of the entities eligible for discounts under the Public Health Service pharmaceutical pricing program;
- requirements to report financial arrangements with physicians, as defined by such law, and teaching hospitals;
- a requirement to annually report drug samples that manufacturers and distributors provide to physicians; and
- a Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research.

There have been executive, judicial and Congressional challenges to repeal or replace certain aspects of the ACA, including measures taken during the former U.S. president's administration. The Trump administration released executive orders and other directives 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. Concurrently, Congress considered legislation that would repeal or repeal and replace all or part of the ACA. While Congress has not passed comprehensive repeal legislation, it has enacted laws that modify certain provisions of the ACA such as removing penalties, since January 1, 2019, for not complying with the ACA's individual mandate to carry health insurance, eliminating the implementation of certain ACA-mandated fees and increasing the point-of-sale discount that is owed by pharmaceutical manufacturers who participate in Medicare Part D. In November 2020, the U.S. Supreme Court held oral arguments on the U.S. Court of Appeals for the Fifth Circuit's decision that held that the individual mandate is unconstitutional. On February 10, 2021, Biden administration withdrew the federal government's support for overturning the ACA. In June 2021, the U.S. Supreme Court remanded the case with instructions to dismiss for lack of standing. However, the U.S. Supreme Court did not decide the ultimate issue of the validity of the individual mandate. Thus, there may be other efforts to challenge the individual mandate or to challenge, repeal or replace the ACA. It is unclear how the U.S. Supreme Court ruling, other such litigation and the healthcare reform measures of the current presidential administration will impact the ACA and our business.

In addition, other legislative changes have been proposed and adopted since the ACA was enacted. On August 2, 2011, the Budget Control Act of 2011 was signed into law, which, among other things, created the Joint Select Committee on Deficit Reduction to recommend to Congress proposals for spending reductions. The Joint Select Committee did not achieve a targeted deficit reduction, triggering the legislation's automatic reduction to several government programs. These changes include aggregate reductions to Medicare payments to providers of up to 2% per fiscal year, which began in 2013, and due to subsequent legislative amendments to the statute, will remain in effect through 2030, with the exception of a temporary suspension from May 1, 2020 through December 31, 2021 due to the COVID-19 pandemic, unless additional Congressional action is taken. In January 2013, the American Taxpayer Relief Act of 2012 was signed into law, which, among other things, reduced Medicare payments to several providers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. These laws may result in additional reductions in Medicare and other healthcare funding.

Further, there has been heightened governmental scrutiny recently over the manner in which drug manufacturers set prices for their marketed products, which has resulted in several Congressional inquiries and proposed and enacted federal and state 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, the former president of the United States used several means to propose or implement drug pricing reform, including through federal budget proposals, executive orders, and policy initiatives. For example, on September 9, 2021, the Biden administration published a wide-ranging list of policy proposals to lower prescription drug prices, including by allowing Medicare to negotiate prices and disincentivizing price increases, and to support market changes that strengthen supply chains, promote biosimilars and generic drugs, and increase price transparency. These initiatives recently culminated in the enactment of the Inflation Reduction Act, or IRA, in August 2022, which will, among other things, allow the U.S. Department of Health and Human Services, or HHS, to negotiate the selling price of certain drugs and biologics that CMS reimburses under Medicare Part B and Part D, although this will only apply to high-expenditure single-source drugs that have been approved for at least 7 years (11 years for biologics). The negotiated prices, which will first become effective in 2026, will be capped at a statutory ceiling price beginning in October 2023, penalize drug manufacturers that increase prices of Medicare Part B and Part D drugs at a rate greater than the rate of inflation. In addition, the law eliminates the "donut hole" under Medicare Part D beginning in 2025 by significantly lowering the beneficiary maximum out-of-pocket cost and requiring manufacturers to subsidize, through a newly established manufacturer discount program, 10% of Part D enrollees' prescription costs for brand drugs below the out-of-pocket maximum, and 20% once the out-of-pocket maximum has been reached. The IRA permits the Secretary of HHS to implement many of these provisions through guidance, as opposed to regulation, for the initial years. Manufacturers that fail to comply with the IRA may be subject to various penalties, including civil monetary penalties. The IRA also extends enhanced subsidies for individuals purchasing health insurance coverage in ACA marketplaces through plan year 2025. These provisions will take effect progressively starting in 2023, although they may be subject to legal challenges. In addition, the Secretary of the HHS recently proposed testing three new models for pricing efficiency, including one that develops payment methods for drugs approved under accelerated approval, in consultation with the Food and Drug Administration, to encourage timely confirmatory trial completion and improve access to post-market safety and efficacy data with the goal of reducing Medicare spending on drugs that have no confirmed

clinical benefit. Further, at the state level, individual states have increasingly passed 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.

We expect that additional state and federal healthcare reform measures will be adopted in the future, particularly in light of the new presidential administration. Such reform measures 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. 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.

Legislative and regulatory proposals have been made to expand post-approval requirements and restrict sales and promotional activities for pharmaceutical products. We cannot be sure whether additional legislative changes will be enacted, or whether the FDA regulations, guidance or interpretations will be changed, or what the impact of such changes on the marketing approvals of our product candidates, if any, may be. In addition, increased scrutiny by the U.S. Congress of the FDA's approval process may significantly delay or prevent marketing approval, as well as subject us to more stringent product labeling and post-marketing testing and other requirements. It is also possible that additional governmental action is taken in response to the ongoing COVID-19 pandemic.

Governments outside of the United States tend to impose strict price controls, which may adversely affect our revenues, if any.

In some countries, including Canada and certain member states of the EU, 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 reimbursement or pricing approval in some countries, we may be required to conduct a clinical trial that compares the cost-effectiveness of our product candidates 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. Political, economic and regulatory developments may further complicate pricing negotiations, and pricing negotiations may continue after reimbursement has been obtained. Reference pricing used by various EU member states, and parallel trade, such as arbitrage between low-priced and high-priced member states, can further reduce prices. There can be no assurance that any country that has price controls or reimbursement limitations for pharmaceutical products will allow favorable reimbursement and pricing arrangements for any products, if approved in those countries. 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 or other countries. In addition, the withdrawal of the United Kingdom, or UK, from its membership in the EU, often referred to as "Brexit," could lead to further legal and regulatory uncertainty in the UK and may lead to the UK and EU adopting divergent laws and regulations, including those related to the pricing of prescription pharmaceuticals, as the UK determines which EU laws to replicate or replace. If the UK were to significantly alter its regulations affecting the pricing of prescription pharmaceuticals, we could face significant new costs. As a result, Brexit could impair our ability to transact business in the EU and the UK.

Laws and regulations governing any international operations we may have in the future may preclude us from developing, manufacturing and selling certain product candidates and products outside of the United States and require us to develop and implement costly compliance programs.

If we expand our operations outside of the United States, we must dedicate additional resources to comply with numerous laws and regulations in each jurisdiction in which we plan to operate. The Foreign Corrupt Practices Act, or FCPA, prohibits any U.S. individual or business and their party agents from paying, offering, authorizing payment or offering anything of value, directly or indirectly, to any foreign official, political party or candidate for the purpose of influencing any act or decision of such third-party in order to assist the individual or business in obtaining or retaining business. The FCPA also obligates companies whose securities are listed in the United States to comply with certain accounting provisions requiring the company to maintain books and records that accurately and fairly reflect all transactions of the company, including international subsidiaries, and to devise and maintain an adequate system of internal accounting controls for international operations.

Compliance with the FCPA is expensive and difficult, particularly in countries in which corruption is a recognized problem. In addition, the FCPA presents particular challenges in the pharmaceutical industry, because, in many countries, hospitals are operated by the government, and doctors and other hospital employees are considered foreign officials.

Various laws, regulations and executive orders also restrict the use and dissemination outside of the United States, or the sharing with certain non-U.S. nationals, of information classified for national security purposes, as well as certain products and technical data relating to those products. We are also subject to U.S. laws and regulations governing export controls, as well as economic sanctions and embargoes on certain countries and persons. If we expand our presence outside of the United States, it will require us to dedicate additional resources to comply with these laws, and these laws may preclude us from developing, manufacturing or selling certain product candidates and products outside of the United States, which could limit our growth potential and increase our development costs.

The failure to comply with laws governing international business practices may result in substantial civil and criminal penalties and suspension or debarment from government contracting. The Securities and Exchange Commission, or the SEC, also may suspend or bar issuers from trading securities on U.S. exchanges for violations of the FCPA's accounting provisions.

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 harm our business.

We and our third-party contractors are subject to numerous foreign, federal, state and local 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. Our operations involve the use of hazardous and flammable materials, including chemicals and biological materials. 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. In the event of contamination or injury resulting from our use of hazardous materials, we could be held liable for any resulting damages, and any liability could exceed our resources, including any available insurance. We could also be held liable for unexpected safety events that could happen in our business offices.

In addition, our leasing and operation of real property may subject us to liability pursuant to certain of these laws or regulations. Under existing U.S. environmental laws and regulations, current or previous owners or operators of real property and entities that disposed or arranged for the disposal of hazardous substances may be held strictly, jointly and severally liable for the cost of investigating or remediating contamination caused by hazardous substance releases, even if they did not know of and were not responsible for the releases.

We could incur significant costs and liabilities which may adversely affect our financial condition and operating results for failure to comply with such laws and regulations, including, among other things, civil or criminal fines and penalties, property damage and personal injury claims, costs associated with upgrades to our facilities or changes to our operating procedures, or injunctions limiting or altering our operations.

Although we maintain liability insurance to cover us for costs and expenses we may incur due to injuries to our employees, 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, hazardous or radioactive 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, which are becoming increasingly more stringent, may impair our research, development or production efforts. Our failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions.

We are subject to certain U.S. and foreign anti-corruption, anti-money laundering, export control, sanctions and other trade laws and regulations. We can face serious consequences for violations.

U.S. and foreign anti-corruption, anti-money laundering, export control, sanctions and other trade laws and regulations prohibit, among other things, companies and their employees, agents, CROs, CMOs, 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 these 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.

Any violations of the laws and regulations described above may result in substantial civil and criminal fines and penalties, imprisonment, the loss of export or import privileges, debarment, tax reassessments, breach of contract and fraud litigation, reputational harm and other consequences.

We are developing our current product candidates, and may continue to develop future product candidates, in combination with other therapies, which would expose us to additional risks.

We are developing our current product candidates in combination with one or more currently approved cancer therapies or therapies in development. Even if any of our current or future product candidates 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 could revoke approval of the therapy used in combination with any of our product candidates, or safety, efficacy, manufacturing or supply issues could arise with these existing therapies. In addition, it is possible that existing therapies with which our product candidates are approved for use could themselves fall out of favor or be relegated to later lines of treatment. This could result in the need to identify other combination therapies for our product candidates or our own products being removed from the market or being less successful commercially.

We may also evaluate our current product candidates in combination with one or more other 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 any product candidate in combination with any such unapproved cancer therapies that do not ultimately obtain marketing approval.

If the FDA or comparable foreign regulatory authorities do not approve or withdraw their approval of these other therapies, or if safety, efficacy, commercial adoption, manufacturing or supply issues arise with the therapies we choose to evaluate in combination with any of our current or future product candidates, we may be unable to obtain approval of or successfully market any one or all of the current or future product candidates we develop. Additionally, if the third-party providers of therapies or therapies in development used in combination with our current or future product candidates are unable to produce sufficient quantities for clinical trials or for commercialization of our current or future product candidates, or if the cost of combination therapies are prohibitive, 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.

We have never commercialized a product candidate as a company before and currently lack the comprehensive, fully staffed expertise, personnel and resources to successfully commercialize any products on our own or together with suitable collaborators.

We have never commercialized a product candidate as a company. We may license certain rights with respect to our product candidates to collaborators and rely on the assistance and guidance of those collaborators. For product candidates for which we retain commercialization rights and marketing approval, we will have to develop our own sales, marketing, market access, commercial planning and supply organization or outsource these activities to a third-party. We are planning on finding collaborations to secure regulatory approvals and commercialize our

products outside of the United States. We cannot assure that any collaboration(s) will result in short-term or long-term benefit to the company.

Factors that may affect our ability to commercialize our product candidates, if approved, on our own include recruiting and retaining adequate numbers of effective sales, marketing, and market access personnel, developing and producing adequate educational and marketing programs to increase public acceptance of our approved product candidates, ensuring regulatory compliance of our company, all communications and materials in the promotional domain, employees and third parties under applicable healthcare laws, and other unforeseen costs associated with creating an independent sales and marketing organization. Developing a sales and marketing organization will be expensive and time-consuming and could delay the launch of our product candidates upon approval. We may not be able to build an effective sales and marketing organization. Alternatively, if we choose to collaborate, either globally or on a territory-by-territory basis, with third parties that have direct sales forces and established distribution systems, either to augment our own sales force and distribution systems or in lieu of our own sales force and distribution systems, we will be required to negotiate and enter into arrangements with such third parties relating to the proposed collaboration and such arrangements may prove to be less profitable than commercializing the product on our own. If we are unable to build our own distribution and marketing capabilities or to find suitable partners for the commercialization of our product candidates, we may not generate revenues from them or be able to reach or sustain profitability.

Risks Related to Our Reliance on Third Parties

We rely, and intend to continue to rely, on third parties to conduct our clinical trials and perform some of our research and potential preclinical studies. If these third parties do not satisfactorily carry out their contractual duties, fail to comply with applicable regulatory requirements or do not meet expected deadlines, our development programs may be delayed or subject to increased costs or we may be unable to obtain regulatory approval, each of which may have an adverse effect on our business, financial condition, results of operations and prospects.

We do not have the ability to independently conduct all aspects of our clinical trials ourselves. As a result, we are dependent on third parties to conduct our ongoing and planned clinical trials of tovorafenib (DAY101) and pimasertib, and any preclinical studies and clinical trials of any future product candidates. The timing of the initiation and completion of these trials will therefore be partially controlled by such third parties and may result in delays to our development programs. Since such third parties partially control the progress of these trials, they may also publish the data related to these trials prior to obtaining or without our approval for doing so. Specifically, we expect CROs, independent clinical investigators and consultants to play a significant role in the conduct of these trials and the subsequent collection and analysis of data. For example, in addition to the Phase 1 clinical trial run by Dana Farber Cancer Institute in collaboration with PNOC, the Children's Oncology Group, a National Cancer Institute-supported clinical trials group and the world's largest organization devoted exclusively to childhood and adolescent cancer research, is developing a group-wide clinical trial of tovorafenib (DAY101) in relapsed Langerhans cell histiocytosis. However, these investigators, CROs and other third parties are not our employees, and we will not be able to control all aspects of their activities. Nevertheless, we are responsible for ensuring that each clinical trial is conducted in accordance with the applicable protocol and legal, regulatory and scientific standards, and our reliance on the investigators, CROs and other third parties does not relieve us of our regulatory responsibilities. We and our CROs are required to comply with GCP requirements, which are regulations and guidelines enforced by the FDA for product candidates in clinical development. Regulatory authorities enforce these GCP requirements through periodic inspections of trial sponsors, clinical trial investigators and clinical trial sites. If we or any of our CROs or clinical trial sites fail to comply with applicable GCP requirements, the data generated in our clinical trials may be deemed unreliable, and the FDA may require us to perform additional clinical trials before approving our marketing applications. We cannot assure you that, upon inspection, the FDA will determine that our clinical trials comply with GCPs. In addition, our clinical trials must be conducted with product produced under cGMP regulations. Our failure or the failure of third parties on whom we rely to comply with these regulations may require us to stop and/or repeat clinical trials, which would delay the marketing approval process.

There is no guarantee that any such CROs, clinical trial investigators or other third parties on which we rely will devote adequate time and resources to our development activities or perform as contractually required. In addition, these third parties may be subject to supply chain or inflationary pressures that limit their ability to achieve anticipated timelines or result a greater cost to us. For example, we are aware of a shortage of non-human primates available for preclinical studies and although that is not expected to impact our current business if we begin new product development programs we could be subject to longer development times or difficulty completing necessary research. If any of these third parties fail to meet expected deadlines, adhere to our clinical protocols or meet regulatory requirements, otherwise perform in a substandard manner, or terminate their engagements with us, the timelines for our development programs may be extended or delayed or our development activities may be suspended or terminated. If our clinical trial site terminates for any reason, we may experience the loss of follow-up information on subjects enrolled in such clinical trial unless we are able to transfer those subjects to another qualified clinical trial site, which may be difficult or impossible.

In addition, with respect to investigator-sponsored trials that may be conducted, we would not control the design or conduct of these trials, and it is possible that the FDA will not view these investigator-sponsored trials as providing adequate support for future clinical trials or market approval, whether controlled by us or third parties, for any one or more reasons, including elements of the design or execution of the trials or safety concerns or other trial results. We expect that such arrangements will provide us certain information rights with respect to the investigator-sponsored trials, including access to and the ability to use and reference the data, including for our own regulatory submissions, resulting from the investigator-sponsored trials. However, we would not have control over the timing and reporting of the data from investigator-sponsored trials, nor would we own the data from the investigator-sponsored trials. If we are unable to confirm or replicate the results from the investigator-sponsored trials or if negative results are obtained, we would likely be further delayed or prevented from advancing further clinical development. Further, if investigators or institutions breach their obligations with respect to the clinical development of our product candidates, or if the data proves to be inadequate compared to the firsthand knowledge we might have gained had the investigator-sponsored trials been sponsored and conducted by us, then our ability to design and conduct any future clinical trials ourselves may be adversely affected. The investigators may design clinical trials with clinical endpoints that are more difficult to achieve, or in other ways that increase the risk of negative clinical trial results compared to clinical trials that we may design on our own. Negative results in investigator-sponsored clinical trials could have a material adverse effect on our efforts to obtain regulatory approval for our product candidates and the public perception of our product candidates. Additionally, the FDA may disagree with the sufficiency of our right of reference to the preclinical, manufacturing or clinical data generated by these investigator-sponsored trials, or our interpretation of preclinical, manufacturing or clinical data from these investigator-sponsored trials. If so, the FDA may require us to obtain and submit additional preclinical, manufacturing, or clinical data.

Furthermore, these third parties may also have relationships with other entities, some of which may be our competitors for whom they may also be conducting clinical trials or other pharmaceutical product development activities that could harm our competitive position. 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 tovorafenib (DAY101), pimasertib or any future product candidates and will not be able to, or may be delayed in our efforts to, successfully commercialize our products.

The manufacture of our product candidates is complex. Our third-party manufacturers may encounter difficulties in production, which could delay or entirely halt their ability to supply our product candidates for clinical trials or, if approved, for commercial sale.

We do not have any manufacturing facilities, and we currently contract with certain third-party manufacturers in China. We rely, and expect to continue to rely, on third parties for the manufacture of our product candidates for clinical testing, product development purposes, to support regulatory application submissions, as well as for commercial manufacture if any of our product candidates obtain marketing approval. In addition, we expect to contract with analytical laboratories for release and stability testing of our product candidates. This reliance on third parties increases the risk that we will not have sufficient quantities of our product candidates or products or such quantities at an acceptable cost or quality, which could delay, prevent or impair our development or commercialization efforts. For example, the extent to which the COVID-19 pandemic impacts our ability to procure sufficient supplies for the development of our product candidates will depend on the severity and duration of the spread of the virus and the actions undertaken to contain the COVID-19 virus or treat its effects. We cannot be sure

if lock-down measures or restrictions will be implemented and what, if any, impact that may have on our facilities and operations in the region, including but not limited to a decrease or disruption of production, increased costs of production or other interruptions in our supply chain. In addition, any disruption in production or inability of our manufacturers specifically in China to produce adequate quantities to meet our needs, whether as a result of a natural disaster or other causes, could impair our ability to operate our business on a day-to-day basis and to continue our development of our product candidates. Furthermore, since these manufacturers are located in China, we are exposed to the possibility of product supply disruption and increased costs in the event of changes in the policies of the United States or Chinese governments, political unrest or unstable economic conditions in China. Any of these matters could materially adversely affect our business, financial condition and results of operations. In addition, disruptions in logistics routes and transportation capabilities could disrupt our supply chain. And, if we experience unexpected spikes in demand over time, we risk running out of our necessary supplies.

We may be unable to establish any agreements with third-party manufacturers or do so on favorable terms. Even if we are able to establish agreements with third-party manufacturers, reliance on third-party manufacturers entails additional risks, including:

- reliance on the third party for regulatory, compliance and quality assurance;
- reliance on the third party for product development, analytical testing, and data generation to support regulatory applications;
- operations of our third-party manufacturers or suppliers could be disrupted by conditions unrelated to our business or operations, including the bankruptcy of the manufacturer or supplier, the issuance of an FDA Form 483 notice or warning letter, or other enforcement action by FDA or other regulatory authority;
- the possible breach of the manufacturing agreement by the third party;
- the possible misappropriation of our proprietary information, including our trade secrets and know-how;
- the possible termination or nonrenewal of the agreement by the third party at a time that is costly or inconvenient for us;
- the possible termination or nonrenewal of the agreement by the third party at a time that is costly or inconvenient for us;
- carrier disruptions or increased costs that are beyond our control; and
- failure to deliver our drugs under specified storage conditions and in a timely manner.

We have only limited supply arrangements in place with respect to our product candidates, and these arrangements do not extend to commercial supply. We acquire all key materials on a purchase order basis. As a result, we do not have long-term committed arrangements with respect to our product candidates and other materials. As a result, supply chain issues, such as those related to certain packaging material, may negatively impact our ability to package and deliver product candidates if not managed effectively. We will need to establish one or more agreements with third parties to develop and scale up the drug manufacturing process, conduct drug testing, and generate data to support a regulatory submission. If we obtain marketing approval for any of our product candidates, we will need to establish an agreement for commercial manufacture with a third party.

Third-party manufacturers may not be able to comply with cGMP regulations or similar regulatory requirements outside of the United States. If the FDA determines that our CMOs are not in compliance with FDA laws and regulations, including those governing cGMPs, the FDA may not approve an NDA until the deficiencies are corrected or we replace the manufacturer in our application with a manufacturer that is in compliance. Moreover, our failure, or the failure of our third-party manufacturers and suppliers, to comply with applicable regulations could result in sanctions being imposed on us, including clinical holds, fines, injunctions, civil penalties, seizures or recalls of product candidates or products, operating restrictions and criminal prosecutions, any of which could significantly and adversely affect supplies of our products. In addition, approved products and the facilities at which they are manufactured are required to maintain ongoing compliance with extensive FDA requirements and the requirements of other similar agencies, including ensuring that quality control and manufacturing procedures conform to cGMP requirements. As such, our CMOs are subject to continual review and periodic inspections to assess compliance with cGMPs. Furthermore, although we do not have day-to-day control over the operations of our CMOs, we are responsible for ensuring compliance with applicable laws and regulations, including cGMPs.

In addition, our third-party manufacturers and suppliers are subject to numerous environmental, health and safety laws and regulations, including those governing the handling, use, storage, treatment and disposal of waste products, and failure to comply with such laws and regulations could result in significant costs associated with civil or criminal fines and penalties for such third parties. Based on the severity of regulatory actions that may be brought against these third parties in the future, our clinical or commercial supply of drug and packaging and other services could be interrupted or limited, which could harm our business.

Our product candidates and any products that we may develop may compete with other product candidates and products for access to manufacturing facilities. As a result, we may not obtain access to these facilities on a priority basis or at all. There are a limited number of manufacturers that operate under cGMP regulations and that might be capable of manufacturing for us.

As we prepare for later-stage clinical trials and potential commercialization, we will need to take steps to increase the scale of production of our product candidates. We have not yet scaled up the manufacturing process for any of our product candidates apart from tovorafenib (DAY101) and may need to scale further to support future supply needs for any of our product candidates. Third-party manufacturers may be unable to successfully increase the manufacturing capacity for any of our product candidates in a timely or cost-effective manner, or at all. In addition, quality issues may arise during scale-up or commercial activities. For example, if microbial, viral or other contaminations are discovered in our product candidates or in the manufacturing facilities in which our product candidates are made, such manufacturing facilities may need to be closed for an extended period of time to investigate and remedy the contamination.

Any performance failure on the part of our existing or future manufacturers could delay clinical development or marketing approval. We do not currently have arrangements in place for redundant supply or a second source for bulk drug substance. If our current CMOs for clinical testing cannot perform as agreed, we may be required to replace such CMOs. Although we believe that there are several potential alternative manufacturers who could manufacture our product candidates, we may incur added costs and delays in identifying and qualifying any such replacement manufacturer or be able to reach agreement with any alternative manufacturer. Further, our third-party manufacturers may experience manufacturing or shipping difficulties due to resource constraints or as a result of natural disasters, labor disputes, unstable political environments, or public health epidemics such as the COVID-19 pandemic. If our current third-party manufacturers cannot perform as agreed, we may be required to replace such manufacturers and we may be unable to replace them on a timely basis or at all.

Our current and anticipated future dependence upon others for the manufacture of our product candidates or products may adversely affect our future profit margins and our ability to commercialize any products that obtain marketing approval on a timely and competitive basis.

We rely on a limited number of suppliers for raw materials and any disruptions arising from our sole suppliers could result in delays in our clinical trials or otherwise adversely affect our business and results of operations.

We rely on a limited number of suppliers, some of whom are our sole source for certain materials, and some of whom are based in foreign jurisdictions. Our small number of suppliers involves a number of additional risks, including risks related to supplier capacity constraints, component availability, price increases, timely delivery, component quality, failure of a key supplier to remain in business and adjust to market conditions, including inflation and changes in interest rates, natural disasters, fire, acts of terrorism, pandemics, including the COVID-19 pandemic, or other catastrophic events. Further, in the case of materials for which we have a sole supplier, even if we are able to replace any raw materials or other materials with an alternative, such alternatives may cost more, result in lower yields or not be as suitable for our purposes. In addition, some of the materials that we use to manufacture our product candidates are complex materials, which may be more difficult to substitute. Therefore, any disruptions arising from our sole suppliers could result in delays and additional regulatory submissions, which may adversely affect our business and results of operations.

We may enter into collaborations with third parties for the development and commercialization of our product candidates. If those collaborations are not successful, we may not be able to capitalize on the market potential of these product candidates.

We may seek third-party collaborators for the development and commercialization of some of our product candidates on a select basis. We have not entered into any collaborations to date. Our likely collaborators for any future collaboration arrangements include large and mid-size pharmaceutical companies, regional and national pharmaceutical companies and biotechnology companies. We face significant competition in seeking appropriate collaborators. Our ability to reach a definitive agreement for a future collaboration will depend, among other things, upon our assessment of the future collaborator's resources and expertise, the terms and conditions of the proposed collaboration and the proposed collaborator's evaluation of a number of factors.

If we do enter into any such arrangements with any third parties, we will likely have limited control over the amount and timing of resources that our future collaborators dedicate to the development or commercialization of our product candidates. Our ability to generate revenues from these arrangements will depend on our future collaborators' abilities and efforts to successfully perform the functions assigned to them in these arrangements. Collaborations with future collaborators involving our product candidates would pose numerous risks to us, including the following:

- collaborators have significant discretion in determining the efforts and resources that they will apply to these collaborations and may not perform their obligations as expected;
- collaborators may de-emphasize or not pursue development and commercialization of our product candidates or may elect not to continue or renew development or commercialization programs based on clinical trial results, changes in the collaborator's strategic focus, including as a result of a sale or disposition of a business unit or development function, or available funding or external factors such as an acquisition that diverts resources or creates competing priorities;
- collaborators may delay clinical trials, provide insufficient funding for a clinical trial program, stop a clinical trial or abandon a product candidate, repeat or conduct new clinical trials or require a new formulation of a product candidate for clinical testing;
- collaborators could independently develop, or develop with third parties, products that compete directly or indirectly with our products or product candidates if the collaborators believe that competitive products are more likely to be successfully developed or can be commercialized under terms that are more economically attractive than ours;
- a collaborator with marketing and distribution rights to multiple products may not commit sufficient resources to the marketing and distribution of our product relative to other products;
- collaborators may not properly obtain, maintain, defend or enforce our intellectual property rights or may use our proprietary information and intellectual property in such a way as to invite litigation or other intellectual property related proceedings that could jeopardize or invalidate our proprietary information and intellectual property or expose us to potential litigation or other intellectual property related proceedings;
- disputes may arise between the collaborators and us that result in the delay or termination of the research, development or commercialization of our products or product candidates or that result in costly litigation or arbitration that diverts management attention and resources;
- 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;
- collaboration agreements may not lead to development or commercialization of product candidates in the most efficient manner or at all; and
- if a future collaborator of ours were to be involved in a business combination, the continued pursuit and emphasis on our product development or commercialization program could be delayed, diminished or terminated.

If we establish one or more collaborations, all of the risks relating to product development, regulatory approval and commercialization described herein would also apply to the activities of any such future collaborators.

Risks Related to Employee Matters and Our Operations

Our future success depends on our ability to retain our executive officers and key employees and to attract, retain and motivate qualified personnel and manage our human capital.

Our ability to compete in the highly competitive biotechnology and pharmaceutical industries depends upon our ability to attract, motivate and retain highly qualified managerial, scientific and medical personnel. We are highly dependent on the development and management expertise of Jeremy Bender, Ph.D., M.B.A., our Chief Executive Officer, Samuel Blackman, M.D., Ph.D., our Chief Medical Officer, as well as the other members of our management team, other key employees and advisors. We currently do not maintain key person insurance on these individuals. Although we have entered into employment agreements with our executive officers, each of them may terminate their employment with us at any time.

Our industry has experienced a high rate of turnover in recent years. Our ability to compete in the highly competitive pharmaceuticals industry depends upon our ability to attract, retain and motivate highly skilled and experienced personnel with scientific, clinical, regulatory, manufacturing and management skills and experience.

We largely conduct our operations in the greater San Francisco Bay Area, a region that is home to other pharmaceutical companies as well as many academic and research institutions, resulting in fierce competition for qualified personnel. We may not be able to attract or retain qualified personnel in the future due to the intense competition for a limited number of qualified personnel among pharmaceutical companies. Many of the other pharmaceutical companies against which we compete have greater financial and other resources, different risk profiles and a longer history in the industry than we do. Our competitors may provide higher compensation, more diverse opportunities and/or better opportunities for career advancement. In addition, as our business changes, key personnel may not want to work for a larger, commercial enterprise. Any or all of these competing factors may limit our ability to continue to attract and retain high quality personnel, which could negatively affect our ability to successfully develop and commercialize our product candidates and to grow our business and operations as currently contemplated. We have adopted a greater level of flexibility in our recruiting practices to attract and hire candidates outside of the San Francisco Bay Area, which is intended to increase retention but could have a negative impact on employee engagement, resulting in greater employee turnover.

We will need to grow the size and capabilities of our organization, and we may experience difficulties in managing this growth.

We had 121 full-time employees as of December 31, 2022. We expect significant growth in the number of our employees and the scope of our operations, particularly in the areas of clinical development, clinical operations, manufacturing, regulatory affairs and, if any of our product candidates receives marketing approval, sales, marketing and distribution. To manage our anticipated future growth, we must continue to implement and improve our managerial, operational and financial systems, expand our facilities and continue to recruit and train additional qualified personnel. Due to our limited financial resources and the limited experience of our management team in managing a company with such anticipated growth and with developing sales, marketing and distribution infrastructure, we may not be able to effectively manage the expansion of our operations or recruit and train additional qualified personnel. The expansion of our operations may lead to significant costs and may divert our management and business development resources.

Further, we currently rely, and for the foreseeable future will continue to rely, in substantial part on certain third-party contract organizations, advisors and consultants to provide certain services, including assuming substantial responsibilities for the conduct of our clinical trials and the manufacture of tovorafenib (DAY101), pimasertib, or any future product candidates. We cannot assure you that the services of such third-party contract organizations, advisors and consultants will continue to be available to us on a timely basis when needed, or that we can find qualified replacements. In addition, if we are unable to effectively manage our outsourced activities or if the quality or accuracy of the services provided by our vendors or consultants is compromised for any reason, our clinical trials may be extended, delayed or terminated, and we may not be able to obtain marketing approval of tovorafenib (DAY101), pimasertib, or any future product candidates or otherwise advance our business. We cannot assure you that we will be able to properly manage our existing vendors or consultants or find other competent outside vendors and consultants on economically reasonable terms, or at all.

If we are not able to effectively manage growth and expand our organization, we may not be able to successfully implement the tasks necessary to further develop and commercialize tovorafenib (DAY101), pimasertib, our other pipeline product candidates or any future product candidates and, accordingly, may not achieve our research, development and commercialization goals.

Our employees, clinical trial investigators, CROs, CMOs, consultants, vendors and any potential 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, clinical trial investigators, CROs, CMOs, consultants, vendors and any potential commercial partners. Misconduct by these parties could include intentional, reckless and/or negligent conduct or disclosure of unauthorized activities to us that violates: (i) FDA regulations or those of comparable foreign regulatory authorities, including those laws that require the reporting of true, complete and accurate information, (ii) manufacturing standards, (iii) federal and state health and data privacy, security, fraud and abuse, government price reporting, transparency reporting requirements, and other healthcare laws and regulations in the United States and abroad, (iv) sexual harassment and other workplace misconduct, or (v) laws that require the true, complete and accurate reporting of financial information or data. 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.

We have adopted a code of conduct applicable to all of our employees, as well as a disclosure program and other applicable policies and procedures, but 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, and we are not successful in defending ourselves or asserting our rights, 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, Medicaid and other federal healthcare programs, contractual damages, reputational harm, diminished profits and future earnings, additional integrity reporting and oversight obligations, and the curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and our results of operations.

If our security measures are compromised, or our information technology systems or those of our CROs, CMOs, vendors, contractors, consultants, or other third-party partners fail or suffer security breaches, cyber-attacks, loss or leakage of data and other disruptions, this could result in a material disruption of our development programs, compromise sensitive information related to our business or other personal information or prevent us from accessing critical information, potentially exposing us to liability, harm our reputation, or otherwise adversely affecting our business.

In the ordinary course of business, we may collect, process, store, and transmit proprietary, confidential, and sensitive information (including but not limited to intellectual property, trade secrets, proprietary business information, personal information, and protected health information, or PHI). It is critical that we do so in a secure manner to maintain the confidentiality, integrity, and availability of such information. We depend on information technology and telecommunications systems for significant elements of our operations and we have installed, and expect to expand, a number of enterprise software systems that affect a broad range of business processes and functional areas, including, for example, systems handling human resources, financial reporting and controls, customer relationship management, regulatory compliance, and other infrastructure operations. We face a number of risks relative to protecting this critical information, including loss of access risk, inappropriate use or disclosure, inappropriate modification, and the risk of our being unable to adequately monitor, audit, and modify our controls over our critical information. This risk extends to the third parties with whom we work, as we rely on a number of third parties to operate our critical business systems and process confidential, proprietary, and sensitive information.

Despite the implementation of security measures, given the size, complexity, and increasing amounts of proprietary, sensitive, and confidential information maintained by our internal information technology systems and those of our CROs, CMOs, vendors, contractors, consultants, and other third-party partners are potentially vulnerable to breakdown, service interruptions, system malfunction, accidents by our personnel or third-party partners, natural disasters, terrorism, global pandemics, war and telecommunication and electrical failures, as well as security breaches from inadvertent or intentional actions by our personnel or those of our CROs, CMOs, vendors, contractors, consultants, business partners and/or other third-party partners, or from cyber-attacks by malicious third parties (including through viruses, worms, malicious code, malware, ransomware, denial-of-service attacks, social engineering and other means to affect service reliability and the confidentiality, integrity and availability of information), which may compromise our system infrastructure, or that of our CROs, CMOs, vendors, contractors, consultants, and other third-party partners, or lead to data leakage.

The risk of a security breach or disruption, particularly through cyber-attacks or cyber intrusion, including by computer hackers, viruses, foreign governments, and cyber terrorists, has generally increased as the number, intensity and sophistication of attempted attacks and intrusions from around the world have increased. The COVID-19 pandemic and the subsequent increase of "work from home" have generally increased the attack surface available for exploitation, as more companies and individuals work online and work remotely, and as such, the risk of a cybersecurity incident potentially occurring, and our investment in risk mitigations against such an incident, is increasing. For example, there has been an increase in phishing and spam emails as well as social engineering attempts from "hackers" hoping to use the COVID-19 pandemic to their advantage. We may not be able to anticipate all types of security threats, nor may we be able to implement preventive measures effective against all such security threats. The techniques used by cyber criminals change frequently, may not be recognized until launched, and can originate from a wide variety of sources, including outside groups such as external service providers, organized crime affiliates, terrorist organizations or hostile foreign governments or agencies. To the extent that any disruption or security breach were to result in a loss of, or damage to, our data or applications, or those of our CROs, CMOs, vendors, contractors, consultants, and other third-party partners, or inappropriate disclosure of confidential, sensitive, or proprietary information, we could incur liability and reputational damage and the further development and commercialization of tovorafenib (DAY101), pimasertib, or any future product candidates could be delayed. Any breach, loss or compromise of proprietary, sensitive, or confidential information may also subject us to civil fines and penalties, including under HIPAA, and other relevant state and federal privacy laws in the United States. For example, the California Consumer Privacy Act of 2018, or the CCPA, as amended by the California Privacy Rights Act, or the CPRA, imposes a private right of action for security breaches that could lead to some form of remedy including regulatory scrutiny, fines, private right of action settlements, and other consequences.

The costs related to significant security breaches or disruptions could be material and exceed the limits of the cybersecurity insurance we maintain against such risks. If the information technology systems of our CROs, CMOs, vendors, contractors, consultants, and other third-party partners become subject to disruptions or security breaches, we may have insufficient recourse against such third parties and we may have to expend significant resources to mitigate the impact of such an event, and to develop and implement protections to prevent future events of this nature from occurring.

We cannot assure you that our data protection efforts and our investment in information technology will prevent significant breakdowns, data leakages, breaches in our systems, or those of our CROs, CMOs, vendors, contractors, consultants, and other third-party partners, or other cyber incidents that could have a material adverse effect upon our reputation, business, operations or financial condition. For example, if such an event were to occur and cause interruptions in our operations, or those of our third-party CROs, CMOs, vendors and other contractors and consultants, 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 tovorafenib (DAY101), pimasertib, or any other 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 those of our third-party CROs, CMOs, vendors and other contractors and consultants, 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 (including trade secrets or other intellectual property, proprietary business information and personal information), which could result in financial, legal, business and reputational harm to us. For example, any such event that leads to unauthorized access, use, or disclosure of personal information, including personal information regarding our clinical trial subjects or personnel, 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, and otherwise subject us to liability under laws and regulations that protect the privacy and security of personal information, which could result in significant legal and financial exposure and reputational damages that could potentially have an adverse effect on our business.

We are required to comply with laws, rules and regulations that require us to maintain the security of personal information. We may have contractual and other legal obligations to notify relevant stakeholders of security breaches. Failure to prevent or mitigate cyber-attacks could result in the unauthorized access to sensitive, confidential, or proprietary information. Most jurisdictions have enacted laws requiring companies to notify individuals, regulatory authorities, and others of security breaches involving certain types of data. In addition, our agreements with CROs, CMOs, vendors, contractors, consultants, and other third-party partners may require us to notify them in the event of a security breach. Such mandatory disclosures are costly, could lead to negative publicity, may cause our customers to lose confidence in the effectiveness of our security measures and require us to expend significant capital and other resources to respond to and/or alleviate problems caused by the actual or perceived security breach.

The costs to respond to a security breach and/or to mitigate any security vulnerabilities that may be identified could be significant, our efforts to address these issues may not be successful, and these issues could result in interruptions, delays, negative publicity, loss of customer trust, diminished use of our products as well as other harms to our business and our competitive position. Remediation of any potential security breach may involve significant time, resources, and expenses. Any security breach may result in regulatory inquiries, litigation or other investigations, and can affect our financial and operational condition.

Litigation resulting from security breaches may adversely affect our business. Unauthorized access to our systems, networks, or physical facilities could result in litigation with our customers or other relevant stakeholders. These proceedings could force us to spend money in defense or settlement, divert management's time and attention, increase our costs of doing business, or adversely affect our reputation.

We may not have adequate insurance coverage for security incidents or breaches, including fines, judgments, settlements, penalties, costs, attorney fees and other impacts that arise out of incidents or breaches. The successful assertion of one or more large claims against us that exceeds available insurance coverage, or results in changes to insurance policies (including premium increases or the imposition of large deductible or co-insurance requirements), could have an adverse effect on our business. In addition, we cannot be sure that our existing insurance coverage and coverage for errors and omissions will continue to be available on acceptable terms or that our insurers will not deny coverage as to any future claim. Our risks are likely to increase as we continue to expand, grow our customer base, and process, store, and transmit increasingly large amounts of proprietary and sensitive data.

We are subject to stringent and changing laws, regulations and standards, and contractual obligations related to privacy, data protection, and data security. The actual or perceived failure to comply with such obligations could lead to government enforcement actions (which could include civil or criminal penalties), fines and sanctions, private litigation and/or adverse publicity and could negatively affect our operating results and business.

We and third parties who we work with are or may become subject to numerous domestic and foreign data protection laws and regulations (i.e., laws and regulations that address privacy and data security), the scope of which are changing, subject to differing applications and interpretations, and may be inconsistent among countries, or conflict with other rules. We are or may become subject to the terms of contractual obligations related to privacy, data protection, and data security. The actual or perceived failure by us or related third parties to comply with such obligations could increase our compliance and operational costs, expose us to regulatory scrutiny, actions, fines and penalties, result in reputational harm, lead to a loss of customers, result in litigation and liability, and otherwise cause a material adverse effect on our business, financial condition, and results of operations.

In the United States, numerous federal and state laws and regulations, including federal health information privacy and security laws, federal and state data breach notification laws, state health information privacy laws and federal and state consumer protection laws (e.g., Section 5 of the Federal Trade Commission Act), that govern the collection, use, disclosure and protection of health-related and other personal information could apply to our operations or the operations of our collaborators. In addition, we may obtain protected health information from third parties (including research institutions from which we obtain clinical trial data) that are subject to privacy and security requirements under HIPAA, as amended by HITECH. Depending on the facts and circumstances, we could be subject to civil and criminal penalties if we obtain, use, or disclose individually identifiable health information maintained by a HIPAA-covered entity in a manner that is not authorized or permitted by HIPAA.

The state of California recently enacted the CCPA, which creates new individual privacy rights for California consumers and places increased privacy and data security obligations on entities handling personal information of consumers or households. The CCPA, in effect since January 1, 2020, and most recently amended by the CPRA, is now in effect as of January 1, 2023 with enforcement beginning on July 1, 2023, subject to the regulations promulgated through a newly created enforcement agency called the California Privacy Protection Agency, or the CPPA. The CCPA gives California residents expanded privacy rights, including the right to request correction, access, and deletion of their personal information, the right to opt out of certain personal information sharing, and the right to receive detailed information about how their personal information is processed, including by California residents' employers. The CCPA and CPRA provide for civil penalties and a private right of action for data breaches that is expected to increase data breach litigation. The CCPA and CPRA may increase our compliance costs and potential liability. The CCPA has prompted several proposals for new federal and state-level privacy legislation, such as in Nevada, New Hampshire, Ohio, New York, Washington, Illinois and Nebraska, as well as in Virginia, which passed the Virginia Consumer Data Protection Act, or VCDPA (effective as of January 1, 2023), and Colorado, which enacted the Colorado Privacy Act, or CoPA, which is set to take effect on July 1, 2023. The VCDPA, CoPA and other such proposed legislation, if enacted, could increase our potential liability and compliance costs, and adversely affect our business.

Foreign data protection laws, including Regulation 2016/679, known as the General Data Protection Regulation, or GDPR, may apply to personal information (including health-related data) obtained from individuals in the European Economic Area, or the EEA, and Switzerland. The GDPR, and its implementing legislation across the EU, imposes strict obligations on businesses, including requiring changes to informed consent practices and more detailed notices for clinical trial subjects and investigators, requiring limitations on data processing, establishing a legal basis for processing personal information, notification of data processing obligations, notification of security incidents to appropriate data protection authorities or data subjects, protecting the security and confidentiality of the personal information, and establishing means for data subjects to exercise rights in relation to their personal information. The GDPR subjects noncompliant companies to fines of up to the greater of 20 million Euros or 4% of their global annual revenues, potential bans on processing of personal information (including clinical trials), and private litigation. To the extent applicable, the GDPR will increase our responsibility and liability in relation to personal information that we process, and we may be required to put in place additional mechanisms and expend additional time and resources to ensure compliance with the EU data protection rules. Additionally, the UK implemented the Data Protection Act effective in May 2018 and statutorily amended in 2019, that substantially implements the GDPR and contains provisions, including UK-specific derogations, for how GDPR is applied in the UK. Changes in these legislations may add additional complexity, variation in requirements, restrictions and potential legal risk, require additional investment in resources for compliance programs, could impact strategies and availability of previously useful data, and could result in increased compliance costs and/or changes in business practices and policies. In addition, supervisory authorities in the EEA, Switzerland, and the UK have enforced data protection legislation inconsistently, which may result in us having to spend additional resources in order to comply with rules and guidance applicable only in certain, local jurisdictions.

Further, European data protection laws generally prohibit the transfer of personal information to countries outside of the EEA, UK, and Switzerland, such as the United States, which are not considered by the European Commission to provide an adequate level of data protection. Switzerland has adopted similar restrictions. Although there are legal mechanisms to allow for the transfer of personal information from the EEA, UK, and Switzerland to the United States and other countries, they are or may become subject to legal challenges that, if successful, could invalidate these mechanisms, restrict our ability to process personal information of Europeans outside of Europe and adversely impact our business. For example, in July 2020, the Court of Justice of the European Union, or CJEU, invalidated the EU-U.S. Privacy Shield, which enabled the transfer of personal information from EU to the U.S. for companies

that had self-certified to the Privacy Shield on the grounds that the EU-U.S. Privacy Shield failed to offer adequate protections to EU personal information transferred to the United States. While the CJEU did not invalidate the use of other data transfer mechanisms, such as the Standard Contractual Clauses, the decision has led to uncertainty regarding the use of such mechanisms for data transfers to the United States, and the CJEU made clear that reliance on Standard Contractual Clauses alone may not necessarily be sufficient in all circumstances. The European Data Protection Board, or EDPB, issued additional guidance regarding the CJEU's decision on November 11, 2020 which imposes higher burdens on the use of data transfer mechanisms, such as the Standard Contractual Clauses, for cross-border data transfers. In June 2021, the European Commission adopted new Standard Contractual Clauses under the GDPR for transfers of personal data outside the EU to countries that the European Commission has not deemed to provide an adequate level of protection for such personal data. If we elect to rely on the new Standard Contractual Clauses for personal data transfers out of the EU, and in light of the EDPB recommendations, we may be required to expend significant resources to meet the obligations the new Standard Contractual Clauses impose; for example, we may be required to conduct transfer impact assessments for such cross-border data transfers and implement additional security measures. We will also have to spend resources to ensure that these new Standard Contractual Clauses continue to be incorporated into all contracts governing data processing and cross-border transfer. In addition, it is anticipated that the UK will finalize its new model clauses governing cross-border data transfers, and therefore we will have to spend additional time and resources seeking to comply with the UK's unique requirements in this area. Due to potential legal challenges, there is uncertainty regarding whether the new EU Standard Contractual Clauses will remain a valid mechanism for transfers of personal information out of the EEA. The use of Standard Contractual Clauses for the transfer of personal information specifically to the United States also remains under review by a number of European data protection supervisory authorities. For example, German and Irish supervisory authorities have indicated that the Standard Contractual Clauses alone provide inadequate protection for EU-U.S. data transfers. Use of the data transfer mechanisms must now be assessed on a case-by-case basis taking into account the legal regime applicable in the destination country, in particular applicable surveillance laws and rights of individuals. To comply with these requirements and as supervisory authorities continue to issue further guidance, we may need to implement additional safeguards to further enhance the security of data transferred out of Europe, we could suffer additional costs, complaints, or regulatory investigations or fines, and if we are otherwise unable to transfer personal information between and among countries and regions in which we operate, it could affect the manner in which we provide our products and services, the geographical location or segregation of our relevant systems and operations, and could adversely affect our financial results.

In addition, further to the UK's exit from the EU on January 31, 2020, the GDPR ceased to apply in the UK at the end of the transition period on December 31, 2020. However, as of January 1, 2021, the United Kingdom's European Union (Withdrawal) Act 2018 incorporated the GDPR (as it existed on December 31, 2020 but subject to certain UK-specific amendments) into UK law, referred to as the UK GDPR. The UK GDPR and the UK Data Protection Act 2018 set out the UK's data protection regime, which is independent from but aligned to the EU's data protection regime. Non-compliance with the UK GDPR may result in monetary penalties of up to £17.5 million or 4% of worldwide revenue, whichever is higher. With respect to transfers of personal data from the EU to the United Kingdom, on June 28, 2021 the European Commission issued an adequacy decision in respect of the UK's data protection framework, enabling data transfers from EU member states to the UK to continue without requiring organizations to put in place contractual or other measures in order to lawfully transfer personal data between the territories. While it is intended to last for at least four years, the European Commission may unilaterally revoke the adequacy decision at any point, and if this occurs it could lead to additional costs and increase our overall risk exposure.

Other countries, including China, Brazil, Australia and Japan, for example, have adopted certain legal requirements for local storage and processing of data and cross-border transfers of personal information, any and all of which could increase the cost and complexity of conducting preclinical testing and clinical trials or delivering our future products, if any, and operating our business. These obligations may be interpreted and applied in a manner that is inconsistent from one jurisdiction to another and may conflict with other requirements or our practices.

We are or may become subject to the terms of external and internal privacy and security policies, representations, certifications, publications related to privacy and security.

Compliance with domestic and foreign privacy, data security, and data protection laws, regulations, and contractual and other obligations could require us to take on more onerous obligations in our contracts, restrict our ability to collect, use and disclose data, or in some cases, impact our ability to operate in certain jurisdictions. The actual or perceived failure to comply with domestic and foreign privacy, data privacy, and data protection laws and regulations could result in government enforcement actions (which could include civil, criminal, and administrative penalties), private litigation and/or adverse publicity and could negatively affect our operating results and business. 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 the information. Claims that we have violated individuals' privacy rights, failed to comply with privacy, data security, and data protection laws, or breached our contractual obligations, even if we are not found liable, could be expensive and time consuming to defend and could result in adverse publicity that could harm our business.

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

Our current operations are primarily located in the San Francisco Bay Area. Any unplanned event, such as earthquake, flood, fire, explosion, extreme weather conditions, medical epidemic or pandemic, power shortage, telecommunication failure or other natural or man-made accident or incident that results in our being unable to fully utilize our facilities, or the manufacturing facilities of our third-party contract manufacturers, may have a material and adverse effect on our ability to operate our business, particularly on a daily basis, and have significant negative consequences on our financial and operating conditions. In addition, the long-term effects of climate change on general economic conditions and the pharmaceutical industry in particular are unclear, and may heighten or intensify existing risk of natural disasters. Loss of access to these facilities may result in increased costs, delays in the development of our product candidates or interruption of our business operations, and have a material adverse effect on our business, financial condition, results of operations and prospects. If a natural disaster, power outage or other event occurred that prevented us from using all or a significant portion of our headquarters, that damaged critical infrastructure such as our research facilities or the manufacturing facilities of our third-party contract manufacturers, or that otherwise disrupted operations, it may be difficult or, in certain cases, impossible, for us to continue our business for a substantial period of time. The disaster recovery and business continuity plans we have in place may prove inadequate in the event of a serious disaster or similar event. We may incur substantial expenses as a result of the limited nature of our disaster recovery and business continuity plans, which could have a material adverse effect on our business. As part of our risk management policy, we maintain insurance coverage at levels that we believe are appropriate for our business. However, in the event of an accident or incident at these facilities, we cannot assure you that the amounts of insurance will be sufficient to satisfy any damages and losses. If our facilities, or the manufacturing facilities of our third-party contract manufacturers, are unable to operate because of an accident or incident or for any other reason, even for a short period of time, any or all of our research and development programs may be harmed. Any business interruption could have a material and adverse effect on our business, financial condition, results of operations and prospects.

Changes in tax laws or regulations that are applied adversely to us may have a material adverse effect on our business, cash flow, financial condition or results of operations.

New income, sales, use or other tax laws, statutes, rules, regulations or ordinances could be enacted at any time, which could adversely affect our business operations and financial performance. Further, existing tax laws, statutes, rules, regulations or ordinances could be interpreted, changed, modified or applied adversely to us. For example, the Tax Cuts and Jobs Act of 2017, or the Tax Cuts and Jobs Act, enacted many significant changes to the U.S. tax laws. Future guidance from the Internal Revenue Service and other tax authorities with respect to the Tax Cuts and Jobs Act may affect us, and certain aspects of the Tax Cuts and Jobs Act could be repealed or modified in future legislation. For example, the CARES Act modified certain provisions of the Tax Cuts and Jobs Act. In addition, it is uncertain if and to what extent various states will conform to the Tax Cuts and Jobs Act, the CARES Act, or any newly enacted federal tax legislation. Changes in corporate tax rates, the realization of net deferred tax assets relating to our operations, the taxation of foreign earnings, and the deductibility of expenses under the Tax Cuts and Jobs Act, the CARES Act or future reform legislation could have a material impact on the value of our deferred tax assets, could result in significant one-time charges, and could increase our future U.S. tax expense.

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

We have incurred substantial losses during our history and do not expect to become profitable in the near future, and we may never achieve profitability. Unused losses incurred in taxable years beginning on or prior to December 31, 2017, will carry forward to offset future taxable income, if any, until such unused losses expire. Under the Tax Cuts and Jobs Act, as modified by the CARES Act, unused U.S. federal net operating losses generated in tax years beginning after December 31, 2017, will not expire and may be carried forward indefinitely but the deductibility of such federal net operating losses in taxable years beginning after December 31, 2020, is limited to 80% of current year taxable income. It is uncertain if and to what extent various states will conform to the Tax Cuts and Jobs Act or the CARES Act. In addition, both our current and our future unused losses and other tax attributes may be subject to limitation under Sections 382 and 383 of the Internal Revenue Code of 1986, as amended, or the Code, if we undergo, or have undergone, an "ownership change," generally defined as a greater than 50 percentage point change (by value) in our equity ownership by certain stockholders over a three-year period. We have not completed a Section 382 study to assess whether an ownership change has occurred or whether there have been multiple ownership changes since our formation due to the complexity and cost associated with such a study and the fact that there may be additional ownership changes in the future. As a result, our net operating loss carryforwards generated in taxable years beginning on or before December 31, 2017, may expire prior to being used, and the deductibility of our net operating loss carryforwards generated in taxable years beginning after December 31, 2017 may be limited, and, if we undergo an ownership change (or if we previously underwent such an ownership change), our ability to use all of our pre-change net operating loss carryforwards and other pre-change tax attributes (such as research tax credits) to offset our post-change income or taxes may be limited. Similar provisions of state tax law may also apply to limit our use of accumulated state tax attributes. In addition, at the state level, 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. As a result, even if we attain profitability, we may be unable to use all or a material portion of our net operating losses and other tax attributes, which could adversely affect our future cash flows.

We have engaged, and will continue to engage, in strategic transactions that could impact our liquidity, increase our expenses and present significant distractions to our management.

We have engaged in strategic transactions, for instance with affiliates of Takeda Pharmaceutical Company Limited, Viracta Therapeutics, Inc. and Merck KGaA, Darmstadt, Germany, and from time to time, we may consider further strategic transactions, such as acquisitions of companies, businesses or assets and out-licensing or in-licensing of products, product candidates or technologies. Additional potential transactions that we may consider include a variety of different business arrangements, including spin-offs, strategic partnerships, joint ventures, restructurings, divestitures, business combinations and investments. Any such transaction may require us to incur non-recurring or other charges, may increase our near term or long-term expenditures and may pose significant integration challenges or disrupt our management or business, which could adversely affect our operations and financial results. For example, these transactions may 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 develop acquired products, product candidates or technologies;
- incurrence of substantial debt or dilutive issuances of equity securities to pay for acquisitions;
- higher than expected acquisition and integration costs;
- write-downs of assets or goodwill or impairment charges;
- increased amortization expenses;
- difficulty and cost in combining the operations, systems and personnel of any acquired businesses with our operations, systems and personnel;
- impairment of relationships with key suppliers or customers of any acquired businesses due to changes in management and ownership; and
- inability to retain key employees of any acquired businesses.

Risks Related to Our Intellectual Property

If we are unable to obtain and maintain patent protection or other necessary rights for our products and technology, or if the scope of the patent protection obtained is not sufficiently broad or our rights under our patents (owned, co-owned or licensed) is not sufficiently broad, our competitors could develop and commercialize products and technology similar or identical to ours, and our ability to successfully commercialize our products and technology may be adversely affected.

Our commercial success depends in part on our ability to obtain and maintain proprietary or intellectual property protection in the United States and other countries for our current product candidates and future products, as well as our core technologies, including our manufacturing know-how. We strive to protect and enhance the proprietary technology, inventions and improvements that are commercially important to the development of our business by seeking, maintaining and defending our intellectual property, whether developed internally or licensed from third parties. We also rely on trade secrets, know-how, continuing technological innovation and in-licensing opportunities to develop, strengthen and maintain our proprietary position in the field of cancer drug development. Additionally, we intend to rely on regulatory protection afforded through rare drug designations, data exclusivity and market exclusivity as well as patent term extensions, where available.

The patent position of biotechnology and pharmaceutical companies generally is highly uncertain, involves complex legal and factual questions, and has in recent years been the subject of much litigation. The degree of patent protection we require to successfully compete in the marketplace may be unavailable or severely limited in some cases and may not adequately protect our rights or permit us to gain or keep any competitive advantage. We cannot provide any assurances that any of our own or licensed patent applications will mature into issued patents, and cannot provide any assurances that any such patents, if issued, will include claims with a scope sufficient to protect our current and future product candidates or otherwise provide any competitive advantage. Additionally, patents can be enforced only in those jurisdictions in which the patent has issued. Furthermore, patents have a limited lifespan. In the United States, the natural expiration of a patent is generally twenty years after its first nonprovisional U.S. filing. The natural expiration of a patent outside of the United States varies in accordance with provisions of applicable local law, but is generally 20 years from the earliest local filing date. Various extensions may be available; however, the life of a patent, and the protection it affords, is limited. 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.

Moreover, our exclusive licenses may be subject to field restrictions and retained rights, which may adversely impact our competitive position. See "Management's Discussion and Analysis of Financial Condition and Results of Operations—Significant Agreements." Our licensed patent portfolio may not provide us with adequate and continuing patent protection sufficient to exclude others from commercializing products similar to our product candidates, including generic versions of such products. In addition, the patent portfolio licensed to us is, or may be, licensed to third parties outside our licensed field, and such third parties may have certain enforcement rights. Thus, patents licensed to us could be put at risk of being invalidated or interpreted narrowly in litigation filed by or against another licensee or in administrative proceedings brought by or against another licensee in response to such litigation or for other reasons.

Other parties have developed technologies that may be related or competitive to our own and such parties may have filed or may file patent applications, or may have received or may receive patents, claiming inventions that may overlap or conflict with those claimed in our own patent applications or issued patents. Publications of discoveries in the scientific literature often lag behind the actual discoveries, and patent applications in the United States and in other jurisdictions are typically not published until 18 months after filing, or in some cases not at all. Therefore, we cannot know with certainty whether the inventors of our patents and applications were the first to make the inventions claimed in those patents or pending patent applications, or that they were the first to file for patent protection of such inventions. Further, we cannot assure you that all of the potentially relevant prior art relating to our patents and patent applications has been found. If such prior art exists, it can invalidate a patent or prevent a patent from issuing from a pending patent application. As a result, the issuance, scope, validity and commercial value of our patent rights cannot be predicted with any certainty. Further, if the breadth or strength of protection provided by our patents and patent applications is threatened, regardless of the outcome, it could dissuade companies from collaborating with us to license, develop or commercialize current or future product candidates.

In addition, the patent prosecution process is expensive and time-consuming, and we or our licensors may not be able to file and prosecute all necessary or desirable patent applications at a reasonable cost or in a timely manner. In addition, the scope of the claims initially submitted for examination may be significantly narrowed by the time they issue, if at all. It is also possible that we or our licensors will fail to identify patentable aspects of our research and development output before it is too late to obtain patent protection. We cannot provide any assurances that we will be able to pursue or obtain additional patent protection based on our research and development efforts, or that any such patents or other intellectual property we generate will provide any competitive advantage. Moreover, we do not have the right to control the preparation, filing and prosecution of patent applications, or to control the maintenance of the patents, covering technology that we license from third parties. Therefore, these patents and applications may not be filed, prosecuted or maintained in a manner consistent with the best interests of our business.

Even if we acquire patent protection that we expect should enable us to maintain competitive advantage, the issuance of a patent is not conclusive as to its inventorship, scope, validity or enforceability. Third parties, including competitors, may challenge the inventorship, scope, validity, or enforceability thereof, which may result in such patents being narrowed, invalidated or held unenforceable. If issued, our patents may be challenged in patent offices in the United States and abroad, or in court. For example, we may be subject to a third-party submission of prior art to the U.S. Patent and Trademark Office, or USPTO, challenging the validity of one or more claims of our patents, once issued. Such submissions may also be made prior to a patent's issuance, precluding the granting of a patent based on one of our patent applications. We may become involved in opposition, reexamination, *inter partes* review, post-grant review, derivation, interference, or similar proceedings in the United States or abroad challenging the claims of our patents, once issued. Furthermore, patents may be challenged in court, once issued. Competitors may claim that they invented the inventions claimed in such patents or patent applications prior to the inventors of our patents, or may have filed patent applications before the inventors of our patents did. A competitor may also claim that we are infringing its patents and that we therefore cannot practice our technology as claimed under our patent applications and patents, if issued. As a result, one or more claims of our patents may be narrowed or invalidated. In litigation, a competitor could claim that our patents, if issued, are not valid for a number of reasons. If a court agrees, we would lose our rights to those challenged patents.

Even if they are unchallenged, our patents and pending patent applications, if issued, may not provide us with any meaningful protection or prevent competitors from designing around our patent claims to circumvent our patents by developing similar or alternative technologies or therapeutics in a non-infringing manner. For example, even if we have a valid and enforceable patent, we may not be able to exclude others from practicing our invention if 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. If the patent protection provided by the patents and patent applications we hold or pursue with respect to our product candidates is not sufficiently broad to impede such competition, our ability to successfully commercialize our product candidates could be negatively affected, which would harm our business. Certain regulatory exclusivities may be available, however, the scope of such regulatory exclusivities is subject to change, and may not provide us with adequate and continuing protection sufficient to exclude others from commercializing products similar to our product candidates.

If the scope of any patent protection we obtain is not sufficiently broad, or if we lose any of our patent protection, our ability to prevent our competitors from commercializing similar or identical product candidates would be adversely affected.

The patent position of biopharmaceutical companies generally is highly uncertain, involves complex legal and factual questions, and has been the subject of much litigation in recent years. As a result, the issuance, scope, validity, enforceability and commercial value of our patent rights are highly uncertain. Our pending and future patent applications and those of our licensors may not result in patents being issued which protect our product candidates or which effectively prevent others from commercializing competitive product candidates.

Moreover, the coverage claimed in a patent application can be significantly reduced before the patent is issued, and its scope can be reinterpreted after issuance. Even if patent applications we own or in-license in the future issue as patents, they may not issue in a form that will provide us with any meaningful protection, prevent competitors or other third parties from competing with us, or otherwise provide us with any competitive advantage. Any patents that we own or in-license may be challenged or circumvented by third parties or may be narrowed or invalidated as a result of challenges by third parties. Consequently, we do not know whether our product candidates will be protectable or remain protected by valid and enforceable patents. Our competitors or other third parties may be able to circumvent our patents or the patents of our licensors by developing similar or alternative technologies or products in a non-infringing manner which could materially adversely affect our business, financial condition, results of operations and prospects.

The issuance of a patent is not conclusive as to its inventorship, scope, validity or enforceability, and our patents or the patents of our licensors may be challenged in the courts or patent offices in the United States and abroad. We may be subject to a third-party pre-issuance submission of prior art to the USPTO, or become involved in opposition, derivation, revocation, reexamination, post-grant review, and *inter partes* review, or other similar proceedings challenging our owned patent rights. An adverse determination in any such submission, proceeding or litigation could reduce the scope of, or invalidate or render unenforceable, our patent rights, allow third parties to commercialize our product candidates and compete directly with us, without payment to us, or result in our inability to manufacture or commercialize products without infringing third-party patent rights. Moreover, our patents or the patents of our licensors may become subject to post-grant challenge proceedings, such as oppositions in a foreign patent office, that challenge our priority of invention or other features of patentability with respect to our patents and patent applications and those of our licensors. Such challenges may result in loss of patent rights, loss of exclusivity or in patent claims being narrowed, invalidated or held unenforceable, 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 product candidates. Such proceedings also may result in substantial cost and require significant time from our scientists and management, even if the eventual outcome is favorable to us. In addition, if the breadth or strength of protection provided by our patents and patent applications or the patents and patent applications of our licensors is threatened, regardless of the outcome, it could dissuade companies from collaborating with us to license, develop or commercialize current or future product candidates.

Furthermore, the issuance of a patent does not give us the right to practice the patented invention. Third parties may have blocking patents that could prevent us from marketing our own patented product and practicing our own patented technology.

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 develop products that are similar to our product candidates but that are not covered by the claims of the patents that we own or license;
- we or our licensors or collaborators might not have been the first to make the inventions covered by the issued patents or patent application that we own or license;
- we or our licensors or 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 the pending patent applications we own or license will not lead to issued patents;
- issued patents that we own or license may be 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;
- the patents of others may have an adverse effect on our business;
- we may fail to adequately protect and police our trademarks and trade secrets; and
- we may choose not to file a patent in order to maintain certain trade secrets or know-how, and a third-party may subsequently file a patent covering such intellectual property.

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

Our commercial success depends significantly on our ability to operate without infringing the patents and other proprietary rights of third parties. Claims by third parties that we infringe their proprietary rights may result in liability for damages or prevent or delay our developmental and commercialization efforts.

Our commercial success depends in part on avoiding infringement of the patents and proprietary rights of third parties. However, our research, development and commercialization activities may be subject to claims that we infringe or otherwise violate patents or other intellectual property rights owned or controlled by third parties. Other entities may have or obtain patents or proprietary rights that could limit our ability to make, use, sell, offer for sale or import our product candidates and products that may be approved in the future, or impair our competitive position. There is a substantial amount of litigation, both within and outside the United States, involving patent and other intellectual property rights in the biopharmaceutical industry, including patent infringement lawsuits, oppositions, reexaminations, inter partes review proceedings and post grant review proceedings before the USPTO and/or corresponding foreign patent offices. Numerous third-party U.S. and foreign issued patents and pending patent applications exist in the fields in which we are developing product candidates. There may be third-party patents or patent applications with claims to materials, formulations, methods of manufacture or methods for treatment related to the use or manufacture of our product candidates.

There may also be patent applications that, if issued as patents, could be asserted against us. Patent applications in the United States and elsewhere are typically published approximately 18 months after the earliest filing for which priority is claimed, with such earliest filing date being commonly referred to as the priority date. Certain U.S. patent applications that will not be filed outside the United States can remain confidential until patents issue. Therefore, patent applications covering our product candidates could have been filed by third parties without our knowledge. Additionally, pending patent applications that have been published can, subject to certain limitations, be later amended in a manner that could cover our product candidates and their uses or manufacturing processes. 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 and can involve other factors such as expert opinion. Our interpretation of the relevance or the scope of claims in a patent or a pending application may be incorrect, which may negatively impact our ability to market our product candidates. Further, we may incorrectly determine that our product candidates and their uses and manufacturing processes are not covered by a third-party patent or may incorrectly predict whether a third-party's pending patent 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, which may negatively impact our ability to develop and market our product candidates. Third-party intellectual property right holders may also actively bring infringement or other intellectual property-related claims against us, even if we have received patent protection for our product candidates and the relevant uses and processes.

As the biopharmaceutical industry expands and more patents are issued, the risk increases that our product candidates may be subject to claims of infringement of the patent rights of third parties. Because patent applications are maintained as confidential for a certain period of time, until the relevant application is published, we may be unaware of third-party patents that may be infringed by commercialization of any of our product candidates, and we cannot be certain that we were the first to file a patent application related to a product candidate or technology. Moreover, 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. In addition, identification of third-party patent rights that may be relevant to our technology is difficult because patent searching is imperfect due to differences in terminology among patents, incomplete databases and the difficulty in assessing the meaning of patent claims. There is also no assurance that there is not prior art of which we are aware, but which we do not believe is relevant to our business, which may, nonetheless, ultimately be found to limit our ability to make, use, sell, offer for sale or import our products that may be approved in the future, or impair our competitive

position. In addition, third parties may obtain patents in the future and claim that use of our technologies infringes upon these patents. Any claims of patent infringement asserted by third parties would be time consuming and could:

- result in costly litigation that may cause negative publicity;
- divert the time and attention of our technical personnel and management;
- cause development delays;
- prevent us from commercializing any of our product candidates until the asserted patent expires or is held finally invalid or not infringed in a court of law;
- require us to develop non-infringing technology, which may not be possible on a cost-effective basis;
- subject us to significant liability to third parties; or
- require us to enter into royalty or licensing agreements, which may not be available on commercially reasonable terms, or at all, or which might be non-exclusive, which could result in our competitors gaining access to the same technology.

Although no third party has asserted a claim of patent infringement against us as of December 31, 2022, others may hold proprietary rights that could prevent our product candidates from being marketed. It is possible that a third-party may assert a claim of patent infringement directed at any of our product candidates. Any patent-related legal action against us claiming damages and seeking to enjoin commercial activities relating to our product candidates, treatment indications, or processes could subject us to significant liability for damages, including treble damages if we were determined to willfully infringe, and require us to obtain a license to manufacture or market our product candidates. Defense of these claims, regardless of their merit, would involve substantial litigation expense and would be a substantial diversion of employee resources from our business. We cannot predict whether we would prevail in any such actions or that any license required under any of these patents would be made available on commercially acceptable terms, if at all. Moreover, even if we or our current and/or future strategic partners were able to obtain a license, the rights may be nonexclusive, which could result in our competitors gaining access to the same intellectual property. In addition, we cannot be certain that we could redesign our product candidates, treatment indications, or processes to avoid infringement, if necessary. Accordingly, an adverse determination in a judicial or administrative proceeding, or the failure to obtain necessary licenses, could prevent us from developing and commercializing our product candidates, which could harm our business, financial condition and operating results. In addition, intellectual property litigation, regardless of its outcome, may cause negative publicity and could prohibit us from marketing or otherwise commercializing our product candidates and technology.

Parties making claims against us may be able to sustain the costs of complex patent litigation more effectively than we can because they have substantially greater resources. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation or administrative proceedings, there is a risk that some of our confidential information could be compromised by disclosure. In addition, any uncertainties resulting from the initiation and continuation of any litigation could have a material adverse effect on our ability to raise additional funds or otherwise have a material adverse effect on our business, results of operations, financial condition and prospects.

Some of our current product candidates and research programs are licensed from third parties. If these license agreements are terminated or interpreted to narrow our rights, our ability to advance our current product candidates or develop new product candidates based on these technologies will be materially adversely affected.

We now depend on, at least in part, Viracta Therapeutics, Inc., Takeda Pharmaceutical Company Limited, Dana Farber Cancer Institute, Millennium Pharmaceuticals, Inc. and Merck KGaA, Darmstadt, Germany, and will continue to depend on Viracta Therapeutics, Inc., Takeda Pharmaceutical Company Limited, Dana Farber Cancer Institute, Millennium Pharmaceuticals, Inc. and Merck KGaA, Darmstadt, Germany and on licenses and sublicenses from other third parties, as well as potentially on other strategic relationships with third parties, for the research, development, manufacturing and commercialization of our current product candidates. If any of our licenses or relationships or any in-licenses on which our licenses are based are terminated or breached, we may:

- lose our rights to develop and market our current product candidates;

- lose patent or trade secret protection for our current product candidates;
- experience significant delays in the development or commercialization of our current product candidates;
- not be able to obtain any other licenses on acceptable terms, if at all; or
- incur liability for damages.

Additionally, even if not terminated or breached, our intellectual property licenses or sublicenses may be subject to disagreements over contract interpretation which could narrow the scope of our rights to the relevant intellectual property or technology or increase our financial or other obligations.

If we experience any of the foregoing, it could have a materially adverse effect on our business and could force us to cease operations which could cause you to lose all of your investment.

If we breach our license agreements, it could have a material adverse effect on our commercialization efforts for our product candidates.

If we breach any of the agreements under which we license the use, development and commercialization rights to our product candidates or technology from third parties, we could lose license rights that are important to our business. Or if we fail to comply with our obligations in the agreements under which we license intellectual property rights from third parties or otherwise experience disruptions to our business relationships with our licensors, we could lose license rights that are important to our business.

Our current lead product candidates are protected by, among other intellectual property rights, patents and patent applications we co-own and exclusively in-license from Viracta Therapeutics, Inc. (f/k/a Sunesis Pharmaceuticals, Inc.). Our current lead product candidates and pipeline and our anticipated near-term pipeline may include technologies, licensed from other third parties, including, for example, Merck KGaA, Darmstadt, Germany.

Under the license agreements, we are subject to various obligations, including diligence obligations such as development and commercialization obligations, as well as potential royalty payments and other obligations. If we fail to comply with any of these obligations or otherwise breach our license agreements, our licensors may have the right to terminate the applicable license in whole or in part. Generally, the loss of any one of our current licenses, or any other license we may acquire in the future, could harm our business, prospects, financial condition and results of operations.

Licensing of intellectual property is of critical importance to our business and involves complex legal, business and scientific issues. Disputes may arise between us and our licensors regarding intellectual property subject to a license agreement, including:

- the scope of rights granted under the license agreement and other interpretation-related issues;
- whether and the extent to which our technology and processes infringe on intellectual property of the licensor that is not subject to the licensing agreement;
- our right to sublicense patent and other intellectual property rights to third parties under collaborative development relationships;
- our diligence obligations with respect to the use of the licensed technology in relation to our development and commercialization of our product candidates, and what activities satisfy those diligence obligations;
- the priority of invention of patented technology;
- the ownership of inventions and know-how resulting from the joint creation or use of intellectual property by our licensors and us and our partners; and
- whether and the extent to which inventors are able to contest the assignment of their rights to our licensors.

If disputes over intellectual property that we have licensed prevent or impair our ability to maintain our current licensing arrangements on acceptable terms or at all, we may be unable to successfully develop and commercialize the affected product candidates. In addition, if disputes arise as to ownership of licensed intellectual property, our ability to pursue or enforce the licensed patent rights may be jeopardized. If we or our licensors fail to adequately protect this intellectual property, our ability to commercialize our products could suffer.

In addition, the agreements under which we license intellectual property or technology from third parties, including our licenses with Viracta Therapeutics, Inc., Takeda Pharmaceutical Company Limited, Dana Farber Cancer Institute, Millennium Pharmaceuticals, Inc. and Merck KGaA, Darmstadt, Germany, 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 license prevent or impair our ability to maintain our licensing arrangements on commercially acceptable terms, we may be unable to successfully develop and commercialize the affected product candidates, which could have a material adverse effect on our business, financial conditions, results of operations, and prospects.

In spite of our best efforts, our licensors might conclude that we materially breached our license agreements and might therefore terminate the license agreements, thereby removing our ability to develop and commercialize products and technology covered by these license agreements. If these in-licenses are terminated, or if the underlying patents fail to provide the intended exclusivity, competitors would have the freedom to seek regulatory approval of, and to market, products identical to ours. This could have a material adverse effect on our competitive position, business, financial conditions, results of operations, and prospects.

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.

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 seek to expand our product candidate pipeline in part by in-licensing the rights to key technologies. The future growth of our business will depend in part on our ability to in-license or otherwise acquire the rights to additional product candidates or technologies. We cannot assure you that we will be able to in-license or acquire the rights to any product candidates or technologies from third parties on acceptable terms or at all.

Other 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 third parties to further develop or commercialize our existing or future 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 existing or future 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 existing or future product candidates could cause us to abandon any related efforts, which could seriously harm our business and operations.

The in-licensing and acquisition of these technologies is a competitive area, and a number of more established companies are also pursuing strategies to license or acquire product candidates or technologies that we may consider attractive. These established companies may have a competitive advantage over us due to their size, cash resources and greater clinical development and commercialization capabilities. In addition, companies that perceive us to be a competitor may be unwilling to license rights to us. Furthermore, we may be unable to identify suitable product candidates or technologies within our area of focus. If we are unable to successfully obtain rights to suitable product candidates or technologies, our business, financial condition and prospects could suffer.

We may be involved in lawsuits to protect or enforce our own patents or our licensors' patents, which could be expensive, time consuming and unsuccessful. Further, our own issued patents or our licensors' patents could be found invalid or unenforceable if challenged in court.

Competitors may infringe our intellectual property rights. To prevent infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time-consuming. In addition, in a patent infringement proceeding, a court may decide that a patent we own or in-license is not valid, is unenforceable and/or

is not infringed. If we or any of our collaborators were to initiate legal proceedings against a third-party to enforce a patent directed at one of our product candidates, the defendant could counterclaim that our patent or the patent of our licensors is invalid and/or unenforceable in whole or in part. In patent litigation in the United States, defendant counterclaims alleging invalidity and/or unenforceability are commonplace. Grounds for a validity challenge include an alleged failure to meet any of several statutory requirements, including lack of novelty, obviousness, lack of sufficient written description, non-enablement, or obviousness-type double patenting. Grounds for an unenforceability assertion could include an allegation that someone connected with prosecution of the patent withheld relevant information from the USPTO or made a misleading statement during prosecution.

Third parties may also raise similar invalidity claims before the USPTO or patent offices abroad, even outside the context of litigation. Such mechanisms include re-examination, inter partes review proceedings, post grant review proceedings, derivation proceedings, and equivalent proceedings in foreign jurisdictions (e.g., opposition proceedings). The outcome following legal assertions of invalidity and/or unenforceability is unpredictable. With respect to the validity question, for example, we cannot be certain that there is no invalidating prior art, of which we, our licensors, and the patent examiners are unaware during prosecution. There is also no assurance that there is not prior art of which we are aware, but which we do not believe affects the validity or enforceability of a claim in our patents and patent applications or the patents and patent applications of our licensors, which may, nonetheless, ultimately be found to affect the validity or enforceability of a claim. If a third-party were to prevail on a legal assertion of invalidity or unenforceability, we would lose at least part, and perhaps all, of the patent protection on our technology, or any product candidates that we may develop. Such a loss of patent protection would have a material adverse impact on our business, financial condition, results of operations and prospects.

In addition, if the breadth or strength of protection provided by our patents and patent applications or the patents and patent applications of our licensors is threatened, it could dissuade companies from collaborating with us to license, develop or commercialize current or future product candidates.

Even if resolved in our favor, litigation or other legal proceedings relating to our intellectual property rights may cause us to incur significant expenses, and could distract our technical and management personnel from their normal responsibilities. Such litigation or proceedings could substantially increase our operating costs 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 conduct such litigation or proceedings adequately. 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. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could compromise our ability to compete in the marketplace.

Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation or other legal proceedings relating to our intellectual property rights, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation or other proceedings.

Intellectual property litigation may lead to unfavorable publicity that harms our reputation and causes the market price of our common shares to decline.

During the course of any intellectual property litigation, there could be public announcements of the initiation of the litigation as well as results of hearings, rulings on motions, and other interim proceedings or developments in the litigation. If securities analysts or investors regard these announcements as negative, the perceived value of our existing product candidates, approved products, programs or intellectual property could be diminished. Accordingly, the market price of shares of our common stock may decline. Such announcements could also harm our reputation or the market for our product candidates, which could have a material adverse effect on our business.

Derivation proceedings may be necessary to determine priority of inventions, and an unfavorable outcome may require us to cease using the related technology or to attempt to license rights from the prevailing party.

Derivation proceedings provoked by third parties or brought by us or declared by the USPTO may be necessary to determine the priority of inventions with respect to our patents or patent applications or those of our licensors. An unfavorable outcome could require us to cease using the related technology or to attempt to license rights to it from the prevailing party. Our business could be harmed if the prevailing party does not offer us a license on commercially reasonable terms. Our defense of derivation proceedings may fail and, even if successful, may result in substantial costs and distract our management and other employees. In addition, the uncertainties associated with

such proceedings could have a material adverse effect on our ability to raise the funds necessary to continue our clinical trials, continue our development programs, license necessary technology from third parties or enter into development or manufacturing partnerships that would help us bring our product candidates to market.

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 stockholders, 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 product development, in-license needed technology, or enter into development partnerships that would help us bring our product candidates to market.

Recent patent reform legislation could increase the uncertainties and costs surrounding the prosecution of our patent applications and/or those of our licensors and the enforcement or defense of our issued patents and/or those of our licensors.

On September 16, 2011, the Leahy-Smith America Invents Act, or the Leahy-Smith Act, was signed into law. The Leahy-Smith Act includes a number of significant changes to U.S. patent law. These include provisions that affect the way patent applications will be prosecuted and may also affect patent litigation. In particular, under the Leahy-Smith Act, the United States transitioned in March 2013 to a "first inventor to file" system in which, assuming that other requirements of patentability are met, the first inventor to file a patent application will be entitled to the patent regardless of whether a third-party was first to invent the claimed invention. A third-party that files a patent application in the USPTO after March 2013 but before us 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. Furthermore, our ability to obtain and maintain valid and enforceable patents depends on whether the differences between our technology and the prior art allow our technology to be patentable over the prior art. Since patent applications in the United States and most other countries are confidential for a period of time after filing or until issuance, we may not be certain that we or our licensors are the first to either (1) file any patent application related to our product candidates or (2) invent any of the inventions claimed in the patents or patent applications.

The Leahy-Smith Act also includes a number of significant changes that affect the way patent applications will be prosecuted and also may affect patent litigation. 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 PGR, IPR, and derivation proceedings. An adverse determination in any such submission or proceeding could reduce the scope or enforceability of, or invalidate, our patent rights, which could adversely affect our competitive position.

Because of a lower evidentiary standard in USPTO proceedings compared to the evidentiary standard in United States 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/or those of our licensors and the enforcement or defense of our issued patents or those of our licensors, all of which could have a material adverse effect on our business, financial condition, results of operations and prospects.

Changes in U.S. patent law, or laws in other countries, could diminish the value of patents in general, thereby impairing our ability to protect our product candidates.

As is the case with other pharmaceutical companies, our success is heavily dependent on intellectual property, particularly patents. Obtaining and enforcing patents in the biopharmaceutical industry involve a high degree of technological and legal complexity. Therefore, obtaining and enforcing biopharmaceutical patents is costly, time consuming and inherently uncertain. Changes in either the patent laws or in the interpretations of patent laws in the United States and other countries may diminish the value of our intellectual property and may increase the uncertainties and costs surrounding the prosecution of patent applications and the enforcement or defense of issued patents. We cannot predict the breadth of claims that may be allowed or enforced in our patents or in third-party patents. In addition, Congress or other foreign legislative bodies may pass patent reform legislation that is unfavorable to us.

For example, 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. In addition to increasing uncertainty with regard to our ability to obtain patents in the future, this combination of events has created uncertainty with respect to the value of patents, once obtained. Depending on decisions by the U.S. Congress, the U.S. federal courts, the USPTO, or similar authorities in foreign jurisdictions, 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 patent and the patents we might obtain or license in the future.

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

We and/or our licensors 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. In addition, we cannot assure you that all inventors have been or will be identified by us and/or by our collaborators despite diligent effort. 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 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. 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.

Patents have a limited lifespan. In the United States, if all maintenance fees are timely paid, the natural expiration of a patent is generally 20 years from its earliest U.S. non-provisional filing date. Various extensions may be available, but the life of a patent, and the protection it affords, is limited. Even if patents covering our product candidates are obtained, once the patent life has expired, we may be open to competition from competitive products. 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. As a result, our patent portfolio may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours.

If we do not obtain patent term extension for our product candidates, our business may be materially harmed.

Depending upon the timing, duration and specifics of FDA marketing approval of our product candidates, one or more of our U.S. patents or those of our licensors may be eligible for limited patent term restoration under the Drug Price Competition and Patent Term Restoration Act of 1984, or the Hatch-Waxman Amendments. The Hatch-Waxman Amendments permit a patent restoration term of up to five years as compensation for patent term lost during product development and the FDA regulatory review process. A maximum of one patent may be extended per FDA approved product as compensation for the patent term lost during the FDA regulatory review process. A patent term extension cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval and only those claims covering such approved drug product, a method for using it or a method for manufacturing it may be extended. Patent term extension may also be available in certain foreign countries upon regulatory approval of our product candidates. However, we may not be granted an extension because of, for example, failing to apply within applicable deadlines, failing to apply prior to expiration of relevant patents or otherwise failing to satisfy applicable requirements. Moreover, the applicable time period or the scope of patent protection afforded could be less than we request. If we are unable to obtain patent term extension or restoration or the term of any such extension is less than we request, our competitors may obtain approval of competing products following our patent expiration, and our revenue could be reduced, possibly materially. Further, if this occurs, our competitors may take advantage of our investment in development and trials by referencing our clinical and preclinical data and launch their product earlier than might otherwise be the case.

We may not be able to protect our intellectual property rights throughout the world.

Although we have pending patent applications in the United States and other countries, filing, prosecuting and defending patents in all countries throughout the world would be prohibitively expensive, and our intellectual property rights in some countries outside the United States can be less extensive than those in the United States. In addition, the laws of some foreign countries do not protect intellectual property rights to the same extent as federal and state laws in the United States. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the United States or from selling or importing products made using our inventions in and into the United States or other jurisdictions. Competitors may use our technologies in jurisdictions where we have not obtained patent protection to develop their own products and, further, may export otherwise infringing products to territories where we have patent protection, but enforcement is not as strong as that in the United States. These products may compete with our product candidates, and our patents, the patents of our licensors, or other intellectual property rights may not be effective or sufficient to prevent them from competing.

Many companies have encountered significant problems in protecting and defending intellectual property rights in foreign jurisdictions. The legal systems of many foreign countries do not favor the enforcement of patents and other intellectual property protection, which could make it difficult for us to stop the infringement of our patents or our licensors' patents or marketing of competing products in violation of our proprietary rights. 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 or the patents of our licensors at risk of being invalidated or interpreted narrowly and our patent applications or the patent applications of our licensors at risk of not issuing and could provoke third parties to assert claims against us. We may not prevail in any lawsuits that we initiate, and the damages or other remedies awarded, if any, may not be commercially meaningful. 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.

Many countries have compulsory licensing laws under which a patent owner may be compelled to grant licenses to third parties. In addition, many countries limit the enforceability of patents against government agencies or government contractors. In these countries, the patent owner may have limited remedies, which could materially diminish the value of such patent. If we are forced to grant a license to third parties with respect to any patents relevant to our business, our competitive position may be impaired, and our business, financial condition, results of operations and prospects may be adversely affected.

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

Periodic maintenance fees, renewal fees, annuity fees and various other governmental fees on patents and/or applications will be due to the USPTO and various foreign patent offices at various points over the lifetime of our patents and/or applications and those of our licensors. We have systems in place to remind us to pay these fees, and we rely on our outside patent annuity service to pay these fees when due. Additionally, the USPTO and various foreign patent offices require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent application process. We employ reputable law firms and other professionals to help us comply, and in many cases, an inadvertent lapse can be cured by payment of a late fee or by other means in accordance with rules applicable to the particular jurisdiction. However, 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. If such an event were to occur, it could have a material adverse effect on our business.

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.

We intend to use registered or unregistered trademarks or trade names to brand and market ourselves and our products. Our trademarks or trade names may be challenged, infringed, circumvented or declared generic or determined to be infringing on other marks. We may not be able to protect our rights to these trademarks and trade names, which we need to build name recognition among potential partners or customers in our markets of interest. At times, competitors 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. Over the long term, if we are unable to establish name recognition based on our trademarks and trade names, then we may not be able to compete effectively, and our business may be adversely affected. Our efforts to enforce or protect our proprietary rights related to trademarks, trade secrets, domain names, copyrights or other intellectual property may be ineffective and could result in substantial costs and diversion of resources and could adversely affect our financial condition or results of operations.

If we are unable to protect the confidentiality of our trade secrets, our business and competitive position would be harmed.

We rely in part on the protection of our trade secrets, including unpatented know-how, technology and other proprietary information to maintain our competitive position. Although we have taken steps to protect our trade secrets and unpatented know-how, including entering into confidentiality agreements with third parties, and confidential information and inventions agreements with employees, consultants and advisors, we cannot provide any assurances that all such agreements have been duly executed, and 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.

Moreover, third parties may still obtain this information or may come upon this or similar information independently, and we would have no right to prevent them from using that technology or information to compete with us. If any of these events occurs or if we otherwise lose protection for our trade secrets, the value of this information may be greatly reduced, and our competitive position would be harmed. If we do not apply for patent protection prior to such publication or if we cannot otherwise maintain the confidentiality of our proprietary technology and other confidential information, then our ability to obtain patent protection or to protect our trade secret information may be jeopardized.

We may be subject to claims that we or our employees have wrongfully used or disclosed alleged confidential information or trade secrets.

We have entered into or may enter in the future into non-disclosure and confidentiality agreements to protect the proprietary positions of third parties, such as outside scientific collaborators, CROs, third-party manufacturers, consultants, advisors, potential partners, and other third parties. We may become subject to litigation where a third party asserts that we or our employees inadvertently or otherwise breached the agreements and used or disclosed trade secrets or other information proprietary to the third parties. Defense of such matters, regardless of their merit, could involve substantial litigation expense and be a substantial diversion of employee resources from our business. We cannot predict whether we would prevail in any such actions. Moreover, intellectual property litigation, regardless of its outcome, may cause negative publicity and could prohibit us from marketing or otherwise commercializing our product candidates and technology. Failure to defend against any such claim could subject us to significant liability for monetary damages or prevent or delay our developmental and commercialization efforts, which could adversely affect our business. Even if we are successful in defending against these claims, litigation could result in substantial costs and be a distraction to our management team and other employees.

Parties making claims against us may be able to sustain the costs of complex intellectual property litigation more effectively than we can because they have substantially greater resources. 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. In addition, any uncertainties resulting from the initiation and continuation of any litigation could have a material adverse effect on our ability to raise additional funds or otherwise have a material adverse effect on our business, operating results, financial condition and prospects.

We may be subject to claims that we have wrongfully hired an employee from a competitor or that we or our employees have wrongfully used or disclosed alleged confidential information or trade secrets of their former employers.

As is common in the biopharmaceutical 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 may become subject to claims that we, our employees or a consultant inadvertently or otherwise used or disclosed trade secrets or other information proprietary to their former employers or their former or current clients. Litigation may be necessary to defend against these claims. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel, which could adversely affect our business. Even if we are successful in defending against these claims, litigation could result in substantial costs and be a distraction to our management team and other employees.

The patent protection and patent prosecution for some of our product candidates may be dependent on third parties.

While we normally seek to obtain the right to control prosecution, maintenance and enforcement of the patents relating to our product candidates, there may be times when the filing and prosecution activities for patents and patent applications relating to our product candidates are controlled by our licensors or collaboration partners. If any of our licensors or collaboration partners fail to prosecute, maintain and enforce such patents and patent applications in a manner consistent with the best interests of our business, including by payment of all applicable fees for patents covering our product candidates, we could lose our rights to the intellectual property or our exclusivity with respect to those rights, our ability to develop and commercialize those product candidates may be adversely affected and we may not be able to prevent competitors from making, using and selling competing products. In addition, even where we have the right to control patent prosecution of patents and patent applications we have licensed from third parties, we may still be adversely affected or prejudiced by actions or inactions of our licensors and their counsel that took place prior to the date upon which we assumed control over patent prosecution.

Currently, our intellectual property protection includes patents and patent applications that we have in-licensed from Viracta Therapeutics, Inc., Takeda Pharmaceutical Company Limited, and Merck KGaA, Darmstadt, Germany. Our exclusive and non-exclusive licenses may be subject to certain retained rights, which may adversely impact our competitive position. We do not control the prosecution and maintenance of several of the licensed patent portfolios; thus, we cannot assure you that the licensed patent families will be prepared, filed, prosecuted, or maintained in a manner consistent with the best interests of our business. See "Management's Discussion and Analysis of Financial Condition and Results of Operations—Significant Agreements." Our licensed patent portfolio may not provide us with adequate and continuing patent protection sufficient to exclude others from commercializing products similar to our product candidates.

Intellectual property discovered through government funded programs may be subject to federal regulations such as "march-in" rights, certain reporting requirements and a preference for U.S.-based companies. Compliance with such regulations may limit our exclusive rights and limit our ability to contract with non-U.S. manufacturers.

Some of our own issued patents or pending patent applications may have been generated through the use of U.S. government funding, and we may acquire or license in the future intellectual property rights that have been generated through the use of U.S. government funding or grants. Pursuant to the Bayh-Dole Act of 1980, the U.S. government has certain rights in inventions developed with government funding. These U.S. government rights include a non-exclusive, non-transferable, irrevocable worldwide license to use inventions for any governmental purpose. In addition, the U.S. government has the right, under certain limited circumstances, to require us to grant exclusive, partially exclusive, or non-exclusive licenses to any of these inventions to a third party if it determines that: (1) adequate steps have not been taken to commercialize the invention; (2) government action is necessary to meet public health or safety needs; or (3) government action is necessary to meet requirements for public use under federal regulations (also referred to as "march-in rights"). If the U.S. government exercised its march-in rights in our existing or future intellectual property rights that are generated through the use of U.S. government funding or grants, we could be forced to license or sublicense intellectual property developed by us or that we license on terms unfavorable to us, and there can be no assurance that we would receive compensation from the U.S. government for the exercise of such rights. The U.S. government also has the right to take title to these inventions if the grant recipient fails to disclose the invention to the government or fails to file an application to register the intellectual property within specified time limits. Intellectual property generated under a government funded program is also subject to certain reporting requirements, compliance with which may require us to expend substantial resources. In addition, the U.S. government requires that any products embodying any of these inventions or produced through the use of any of these inventions be manufactured substantially in the United States. This preference for U.S. industry may be waived by the federal agency that provided the funding if the owner or assignee of the intellectual property can show that reasonable but unsuccessful efforts have been made to grant licenses on similar terms to potential licensees that would be likely to manufacture substantially in the United States or that under the circumstances domestic manufacture is not commercially feasible. This preference for U.S. industry may limit our ability to contract with non-U.S. product manufacturers for products covered by such intellectual property.

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.

Geo-political actions in the United States and in foreign countries could increase the uncertainties and costs surrounding the prosecution or maintenance of our patent applications or those of any current or future licensors and the maintenance, enforcement or defense of our issued patents or those of any current or future licensors.

For example, the United States and foreign government actions related to Russia's invasion of Ukraine may limit or prevent filing, prosecution and maintenance of patent applications in Russia. Government actions may also prevent maintenance of issued patents in Russia. These actions could result in abandonment or lapse of our patents or patent applications, resulting in partial or complete loss of patent rights in Russia. If such an event were to occur, it could have a material adverse effect on our business. In addition, a decree was adopted by the Russian government in March 2022, allowing Russian companies and individuals to exploit inventions owned by patentees that have citizenship or nationality in, are registered in, or have predominately primary place of business or profit-making activities in the United States and other countries that Russia has deemed unfriendly without consent or compensation. Consequently, we would not be able to prevent third parties from practicing our inventions in Russia or from selling or importing products made using our inventions in and into Russia. Accordingly, our competitive position may be impaired, and our business, financial condition, results of operations and prospects may be adversely affected.

Risks Related to Our Common Stock

An active and liquid trading market for our common stock may never be sustained. As a result, you may not be able to resell your shares of common stock at or above the purchase price.

An active trading market for our common stock may never be sustained. The market value of our common stock may decrease from the purchase price. As a result of these and other factors, you may be unable to resell your shares of our common stock at or above the purchase price. The lack of an active market may impair your ability to sell your shares at the time you wish to sell them or at a price that you consider reasonable. The lack of an active market may also reduce the fair market value of your shares.

Furthermore, an inactive market may also impair our ability to raise capital by selling shares of our common stock and may impair our ability to enter into strategic collaborations or acquire companies or products by using our shares of common stock as consideration.

Our quarterly operating results may fluctuate significantly or may fall below the expectations of investors or securities analysts, each of which may cause our stock price to fluctuate or decline.

We expect our operating results to be subject to quarterly fluctuations. Our net loss and other operating results will be affected by numerous factors, including:

- timing and variations in the level of expense related to the current or future development of our programs;
- timing and status of enrollment for our clinical trials;
- results of clinical trials, or the addition or termination of clinical trials or funding support by us or potential future partners;
- our execution of any collaboration, licensing or similar arrangements, and the timing of payments we may make or receive under potential future arrangements or the termination or modification of any such potential future arrangements;

- any intellectual property infringement, misappropriation or violation lawsuit or opposition, interference or cancellation proceeding in which we may become involved;
- additions and departures of key personnel;
- strategic decisions by us or our competitors, such as acquisitions, divestitures, spin-offs, joint ventures, strategic investments or changes in business strategy;
- if any product candidate we may develop receive regulatory approval, the timing and terms of such approval and market acceptance and demand for such product candidates;
- the timing and cost to establish a sales, marketing and distribution infrastructure to commercialize any products for which we may obtain marketing approval and intend to commercialize on our own or jointly with future collaborators;
- regulatory developments affecting current or future product candidates or those of our competitors;
- the amount of expense or gain associated with the change in value of the success payments and contingent consideration;
- changes in general market and economic conditions, such as due to rising interest rates, inflation, the war in Ukraine and the recent COVID-19 pandemic; and
- business development activities, such as additional program in-licensing, which could result in up-front payments or increased development expenses.

If our quarterly operating results fall below the expectations of investors or securities analysts, the price of our common stock could decline substantially. Furthermore, any quarterly fluctuations in our operating results may, in turn, cause the price of our common stock to fluctuate substantially. We believe that quarterly comparisons of our financial results are not necessarily meaningful and should not be relied upon as an indication of our future performance.

The market price of our common stock is likely to be highly volatile, which could result in substantial losses for purchasers of our common stock.

The market price of our common stock is likely to continue to be highly volatile and subject to wide fluctuations in response to various factors, some of which we cannot control. As a result of this volatility, you may not be able to sell your shares of common stock at or above the price paid. The market price for our common stock may be influenced by many factors, including the other risks described in this "Risk Factors" section and the following:

- results of preclinical studies or clinical trials by us or those of our competitors or by existing or future collaborators or licensing partners;
- the timing and enrollment status of our clinical trials;
- changes in the development status of our product candidates, including variations in the level of expense related to the development of our programs or funding support by us or by existing or future collaborators or licensing partners;
- regulatory or legal developments in the United States and other countries, especially changes in laws or regulations applicable to our business;
- the success of competitive products or technologies;
- introductions and announcements of new product candidates by us, our future collaboration partners, or our competitors, and the timing of these introductions or announcements;
- actions taken by regulatory agencies with respect to our product candidates, clinical studies, manufacturing process or sales and marketing terms;
- our execution of any collaboration, licensing or similar arrangements, and the timing of payments we may make or receive under existing or future arrangements or the termination or modification of any such existing or future arrangements;

- actual or anticipated variations in our financial results or those of companies that are perceived to be similar to us;
- the success of our efforts to acquire or in-license additional technologies or product candidates;
- announced or completed significant acquisitions, strategic collaborations, joint ventures or capital commitments by us or our competitors;
- developments or disputes concerning our intellectual property and proprietary rights;
- the recruitment or departure of key personnel;
- changes in the structure of healthcare payment systems;
- actual or anticipated changes in earnings estimates or changes in stock market analyst recommendations regarding our common stock, other comparable companies or our industry generally;
- our failure or the failure of our competitors to meet analysts' projections or guidance that we or our competitors may give to the market;
- speculation in the press or investment community;
- share price and fluctuations of trading volume of our common stock;
- the impact of interest rate increases on the overall stock market and the market for biopharmaceutical company stocks;
- fluctuations in the valuation of companies perceived by investors to be comparable to us;
- sales of shares of our common stock by us, insiders or our stockholders;
- our ability or inability to raise additional capital and the terms on which we raise it;
- the concentrated ownership of our common stock;
- changes in accounting principles;
- natural disasters, terrorist acts, acts of war and other calamities;
- general economic, industry and market conditions, including rising interest rates and inflation, many of which are beyond our control; and
- other events or factors, including those resulting from global pandemics, such as the COVID-19 pandemic, or war, incidents of terrorism or responses to these events, including those related to the war in Ukraine.

In addition, the stock market in general, and the markets for pharmaceutical, biopharmaceutical and biotechnology stocks in particular, have experienced extreme price and volume fluctuations, including as a result of the COVID-19 pandemic, increase in inflation and changes in interest rates, and disruptions to the supply chain, that have been often unrelated or disproportionate to the operating performance of the issuer. Furthermore, the trading price of our common stock may be adversely affected by third parties trying to drive down the market price. Short sellers and others, some of whom post anonymously on social media, may be positioned to profit if our stock declines and their activities can negatively affect our stock price. These broad market and industry factors may seriously harm the market price of our common stock, regardless of our actual operating performance. The realization of any of the above risks or any of a broad range of other risks, including those described in this "Risk Factors" section, could have a dramatic and adverse impact on the market price of our common stock.

In the past, securities class action litigation has often been brought against public companies following declines in the market price of their securities. This risk is especially relevant for biopharmaceutical companies, which 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 our resources, which could harm our business.

We do not currently intend to pay dividends on our common stock and, consequently, our stockholders' ability to achieve a return on their investment will depend on appreciation of the value of our common stock.

We have never declared or paid cash dividends on our common stock. We currently intend to retain all available funds and any future earnings to support operations and to finance the growth and development of our business. We do not intend to declare or pay any cash dividends on our capital stock in the foreseeable future. As a result, any investment return on our common stock will depend upon increases in the value for our common stock, which is not certain.

A sale of a substantial number of shares of our common stock may cause the price of our common stock to decline.

Sales of a substantial number of shares of our common stock in the public market could occur at any time. If our stockholders sell, or the market perceives that our stockholders intend to sell, substantial amounts of our common stock in the public market, the market price of our common stock could decline significantly.

The holders of an aggregate of 73,458,176 shares of our outstanding common stock as of December 31, 2022 will have rights, subject to some conditions, to require us to file registration statements covering their shares or to include their shares in registration statements that we may file for ourselves or our stockholders. We also have registered shares of common stock that we may issue under our equity incentive plans. These shares are freely tradeable in the public market upon issuance.

We cannot predict what effect, if any, sales of our shares in the public market or the availability of shares for sale will have on the market price of our common stock. However, future sales of substantial amounts of our common stock in the public market, including shares issued upon exercise of our outstanding options, or the perception that such sales may occur, could adversely affect the market price of our common stock.

We also expect that significant additional capital may be needed in the future to continue our planned operations. To raise capital, we may sell common stock, convertible securities or other equity securities in one or more transactions at prices and in a manner we determine from time to time. To the extent that additional capital is raised through the sale and issuance of shares or other securities convertible into shares, our stockholders will be diluted. These sales, or the perception in the market that the holders of a large number of shares intend to sell shares, could reduce the market price of our common stock.

Our principal stockholders and management own a significant percentage of our stock and will be able to exert significant control over matters subject to stockholder approval.

Based on the beneficial ownership of our common stock as of December 31, 2022, our executive officers, directors, holders of 5% or more of our capital stock and their respective affiliates beneficially owned 34% of our voting stock. The voting power of this group may increase to the extent they convert shares of non-voting common stock they hold into common stock. As a result, these stockholders, if acting together, will continue to have significant influence over the outcome of corporate actions requiring stockholder approval, including the election of directors, amendment of our organizational documents, any merger, consolidation or sale of all or substantially all of our assets and any other significant corporate transaction. The interests of these stockholders may not be the same as or may even conflict with your interests. For example, these stockholders could delay or prevent a change of control of our company, even if such a change of control would benefit our other stockholders, which could deprive our stockholders of an opportunity to receive a premium for their common stock as part of a sale of our company or our assets and might affect the prevailing market price of our common stock.

We are an "emerging growth company" and a "smaller reporting company" and we cannot be certain if the reduced reporting requirements applicable to emerging growth companies or smaller reporting companies will make our common stock 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 (i) not being required to comply with the auditor attestation requirements of the Sarbanes-Oxley Act, (ii) reduced disclosure obligations regarding executive compensation in our periodic reports and proxy statements and (iii) exemptions from the requirements of holding

nonbinding advisory stockholder votes on executive compensation and stockholder approval of any golden parachute payments not approved previously.

We could be an emerging growth company for up to five fiscal years following the completion of the IPO; *provided*, *however*, certain circumstances could cause us to lose that status earlier, including if we are deemed to be a "large accelerated filer," which occurs when the market value of our common stock that is held by non-affiliates equals or exceeds $700 million, if we have total annual gross revenue of $1.235 billion or more, or if we issue more than $1.0 billion in non-convertible debt during any three-year period before that time. As of December 31, 2023, we will lose our status as an emerging growth company and will no longer be able to take advantage of the exemptions from various reporting requirements, beginning with our annual report for the fiscal year ending December 31, 2023, to be filed in 2024.

Even after we no longer qualify as an emerging growth company, we may still qualify as a "smaller reporting company," which would allow us to take advantage of many of the same exemptions from disclosure requirements, including not being required to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act and reduced disclosure obligations regarding executive compensation in our periodic reports and proxy statements. We cannot predict if investors will find our common stock less attractive because we may rely on these exemptions. If some investors find our common stock less attractive as a result, there may be a less active trading market for our common stock and our share price may be more volatile.

Under the JOBS Act, emerging growth companies can also delay adopting new or revised accounting standards until such time as those standards apply to private companies. We have elected to take advantage of the benefits of this extended transition period. Our financial statements may therefore not be comparable to those of companies that comply with such new or revised accounting standards. Until the date that we are no longer an "emerging growth company" or affirmatively and irrevocably opt out of the exemption provided by Section 7(a)(2)(B) of the Securities Act, upon issuance of a new or revised accounting standard that applies to our consolidated financial statements and that has a different effective date for public and private companies, we will disclose the date on which adoption is required for non-emerging growth companies and the date on which we will adopt the recently issued accounting standard.

We are also a "smaller reporting company," meaning that the market value of our stock held by non-affiliates is less than $700.0 million and our annual revenue is less than $100.0 million during the most recently completed fiscal year. We may continue to be a smaller reporting company if either (i) the market value of our stock held by non-affiliates is less than $250.0 million or (ii) our annual revenue is less than $100.0 million during the most recently completed fiscal year and the market value of our stock held by non-affiliates is less than $700.0 million. If we are a smaller reporting company at the time we cease to be an emerging growth company, we may continue to rely on the same exemptions from certain disclosure requirements, including not being required to comply with the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act, reduced disclosure obligations regarding executive compensation and the option to present only the two most recent fiscal years of audited financial statements in our Annual Report on Form 10-K. We cannot predict if investors will find our common stock less attractive because we may rely on these exemptions. If some investors find our common stock less attractive as a result, there may be a less active trading market for our common stock and our share price may be more volatile.

Anti-takeover provisions in our charter documents and under Delaware law could prevent or delay an acquisition of us, which may be beneficial to our stockholders, and may prevent attempts by our stockholders to replace or remove our current management.

Our restated certificate of incorporation and our amended and restated bylaws contain provisions that could delay or prevent a change in control of our company. These provisions could also make it difficult for stockholders to elect directors who are not nominated by current members of our board of directors or take other corporate actions, including effecting changes in our management. These provisions:

- establish a classified board of directors so that not all members of our board are elected at one time;
- permit only the board of directors to establish the number of directors and fill vacancies on the board;
- provide that directors may only be removed "for cause" and only with the approval of two-thirds of our stockholders;

- require super-majority voting to amend some provisions in our restated certificate of incorporation and restated bylaws;
- authorize the issuance of "blank check" preferred stock that our board could use to implement a stockholder rights plan;
- eliminate the ability of our stockholders to call special meetings of stockholders;
- prohibit stockholder action by written consent, which requires all stockholder actions to be taken at a meeting of our stockholders;
- prohibit cumulative voting; and
- establish advance notice requirements for nominations for election to our board or for proposing matters that can be acted upon by stockholders at annual stockholder meetings.

In addition, Section 203 of the Delaware General Corporation Law, or DGCL, may discourage, delay or prevent a change in control of our company. Section 203 imposes certain restrictions on mergers, business combinations and other transactions between us and holders of 15% or more of our common stock.

The exclusive forum provision in our organizational documents may limit a stockholder's ability to bring a claim in a judicial forum that it finds favorable for disputes with us or any of our directors, officers, or other employees, or the underwriters of any offering giving rise to such claim, which may discourage lawsuits with respect to such claims.

Our restated certificate of incorporation provides that, to the fullest extent permitted by law, the Court of Chancery of the State of Delaware is the exclusive forum for: any derivative action or proceeding brought on our behalf; any action asserting a breach of fiduciary duty; any action asserting a claim against us arising pursuant to the DGCL, our restated certificate of incorporation, or our restated bylaws; or any action asserting a claim against us that is governed by the internal affairs doctrine. This exclusive forum provision does not apply to suits brought to enforce a duty or liability created by the Securities Exchange Act of 1934, as amended, or the Exchange Act. It could apply, however, to a suit that falls within one or more of the categories enumerated in the exclusive forum provision.

This choice of forum provision may limit a stockholder's ability to bring a claim in a judicial forum that it finds favorable for disputes with us or any of our directors, officers, or other employees, or the underwriters of any offering giving rise to such claims, which may discourage lawsuits with respect to such claims. Alternatively, if a court were to find the choice of forum provisions contained in our restated certificate of incorporation to be inapplicable or unenforceable in an action, we may incur additional costs associated with resolving such action in other jurisdictions, which could harm our business, results of operations and financial condition.

Section 22 of the Securities Act creates concurrent jurisdiction for federal and state courts over all claims brought to enforce any duty or liability created by the Securities Act or the rules and regulations thereunder. Our restated bylaws will provide that the federal district courts of the United States of America will, to the fullest extent permitted by law, be the exclusive forum for resolving any complaint asserting a cause of action arising under the Securities Act, or a Federal Forum Provision, including for all causes of action asserted against any defendant named in such complaint. For the avoidance of doubt, this provision is intended to benefit and may be enforced by us, our officers and directors, the underwriters to any offering giving rise to such complaint, and any other professional entity whose profession gives authority to a statement made by that person or entity and who has prepared or certified any part of the documents underlying the offering. Our decision to adopt a Federal Forum Provision followed a decision by the Supreme Court of the State of Delaware holding that such provisions are facially valid under Delaware law. While federal or state courts may not follow the holding of the Delaware Supreme Court or may determine that the Federal Forum Provision should be enforced in a particular case, application of the Federal Forum Provision means that suits brought by our stockholders to enforce any duty or liability created by the Securities Act must be brought in federal court and cannot be brought in state court, and our stockholders cannot waive compliance with the federal securities laws and the rules and regulations thereunder.

Section 27 of the Exchange Act creates exclusive federal jurisdiction over all claims brought to enforce any duty or liability created by the Exchange Act or the rules and regulations thereunder. In addition, neither the exclusive forum provision nor the Federal Forum Provision applies to suits brought to enforce any duty or liability created by the Exchange Act. Accordingly, actions by our stockholders to enforce any duty or liability created by the Exchange

Act or the rules and regulations thereunder must be brought in federal court, and our stockholders cannot waive compliance with the federal securities laws and the rules and regulations thereunder.

Any person or entity purchasing or otherwise acquiring or holding any interest in any of our securities shall be deemed to have notice of and consented to our exclusive forum provisions, including the Federal Forum Provision. These provisions may limit a stockholders' ability to bring a claim and may result in increased costs for a stockholder to bring such a claim, in a judicial forum of their choosing for disputes with us or our directors, officers, or other employees, or the underwriters of any offering giving rise to such claim, which may discourage lawsuits against us and our directors, officers, and other employees.

If securities or industry analysts do not publish research or reports about our business, or if they issue an adverse or misleading opinion regarding our company, our common stock price and trading volume could decline.

The trading market for our common stock is influenced by the research and reports that industry or securities analysts publish about us or our business. We do not have any control over the analysts, or the content and opinions included in their reports. If any of the analysts who cover us issue an adverse or misleading opinion regarding us, our business model, our intellectual property or our stock performance, or if our preclinical studies and future clinical trials and operating results fail to meet the expectations of analysts, our stock price would likely decline. If one or more of such analysts cease coverage of us or fail to publish reports on us regularly, we could lose visibility in the financial markets, which in turn could cause a decline in our stock price or trading volume.

General Risk Factors

We will incur increased costs as a result of operating as a public company, and our management will be required to devote substantial time to new compliance initiatives and corporate governance practices.

As a public company, and particularly after we are no longer an emerging growth company, we will incur significant legal, accounting and other expenses that we did not incur as a private company. The Sarbanes-Oxley Act, the Dodd-Frank Wall Street Reform and Consumer Protection Act, the listing requirements of the Nasdaq Global Select Market, or Nasdaq, and other applicable securities rules and regulations impose various requirements on public companies, including establishment and maintenance of effective disclosure and financial controls and corporate governance practices. Our management and other personnel will need to devote a substantial amount of time to these compliance initiatives. Moreover, we expect these rules and regulations to substantially increase our legal and financial compliance costs and to make some activities more time consuming and costly. For example, we expect that these rules and regulations may make it more difficult and more expensive for us to obtain director and officer liability insurance and we may be required to incur substantial costs to maintain sufficient coverage. We cannot predict or estimate the amount or timing of additional costs we may incur to respond to these requirements. The impact of these requirements could also make it more difficult for us to attract and retain qualified persons to serve on our board of directors, our board committees or as executive officers. The increased costs may require us to reduce costs in other areas of our business or increase the prices of our products once commercialized. Moreover, these rules and regulations are often subject to varying interpretations, in many cases due to their lack of specificity, and, as a result, their application in practice may evolve over time as new guidance is provided by regulatory and governing bodies. This could result in continuing uncertainty regarding compliance matters and higher costs necessitated by ongoing revisions to disclosure and governance practices.

If we fail to maintain proper and effective internal controls over financial reporting our ability to produce accurate and timely financial statements could be impaired.

Pursuant to Section 404 of the Sarbanes-Oxley Act, our management is required to report upon the effectiveness of our internal control over financial reporting beginning with this Annual Report on Form 10-K for the year ended December 31, 2022. When we lose our status as an "emerging growth company" and become an "accelerated filer" or a "large accelerated filer," our independent registered public accounting firm will be required to attest to the effectiveness of our internal control over financial reporting. The rules governing the standards that must be met for management to assess our internal control over financial reporting are complex and require significant documentation, testing, and possible remediation. To achieve compliance with Section 404 within the prescribed

period, we will be engaged in a process to document and evaluate our internal control over financial reporting, which is both costly and challenging. In this regard, we will need to continue to dedicate internal resources, potentially engage outside consultants and adopt a detailed work plan to assess and document the adequacy of internal control over financial reporting, continue steps to improve control processes as appropriate, validate through testing that controls are functioning as documented and implement a continuous reporting and improvement process for internal control over financial reporting. This process will be time-consuming, costly and complicated.

Any failure to maintain internal control over financial reporting could severely inhibit our ability to accurately report our financial condition, results of operations, or cash flows. If we are unable to conclude that our internal control over financial reporting is effective, or if our independent registered public accounting firm determines we have a material weakness or significant deficiency in our internal control over financial reporting, investors may lose confidence in the accuracy and completeness of our financial reports, the market price of our common stock could decline, and we could be subject to sanctions or investigations by the Nasdaq Global Select Market, or Nasdaq, the SEC, or other regulatory authorities. Failure to remedy any material weakness in our internal control over financial reporting, or to implement or maintain other effective control systems required of public companies, could also restrict our future access to the capital markets.

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. In addition, we do not have a formal risk management program for identifying and addressing risks to our business in other areas.

We may be subject to securities litigation, which is expensive and could divert management attention.

The market price of our common stock may be volatile. The stock market in general, and Nasdaq and biopharmaceutical companies in particular, have experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of these companies. In the past, companies that have experienced volatility in the market price of their stock have been subject to securities class action litigation. We may be the target of this type of litigation in the future. Securities litigation against us could result in substantial costs and divert our management's attention from other business concerns, which could seriously harm our business.

Item 1B. Unresolved Staff Comments.

None.

Item 2. Properties.

Our principal executive office is located in Brisbane, California, where we lease approximately 12,000 square feet of office space. The lease expires in December 2024. There is no option to extend the lease term nor is there an option to terminate the lease prior to its expiration. We believe these facilities are sufficient to meet our ongoing needs and that, if we require additional space, we will be able to obtain additional facilities on commercially reasonable terms.

Item 3. Legal Proceedings.

The Company, from time to time, may be party to litigation arising in the ordinary course of business. The Company is not subject to any material legal proceedings, and to the best of its knowledge, no material legal proceedings are currently pending or threatened.

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 for Common Stock

We became a public company on May 26, 2021. Our Common Stock is listed for trading on the NASDAQ Capital Market under the symbol "DAWN."

Holders of Record

As of March 1, 2023, there were approximately 36 stockholders of record of our common stock based on information provided by our transfer agent. The actual number of stockholders is greater than this number of record holders, and includes stockholders who are beneficial owners, but whose shares are held in street name by brokers and other nominees. This number of holders of record also does not include stockholders whose shares may be held in trust by other entities.

Dividend Policy

We have never declared or paid cash or stock dividends on our common stock. We currently intend to retain all available funds and any future earnings for use in the operation of our business and do not anticipate paying any dividends on our common stock in the foreseeable future. Any future determination to declare dividends on common stock will be made at the discretion of our board of directors and will depend on our financial condition, operating results, capital requirements, general business conditions and other factors that our board of directors may deem relevant.

Securities Authorized for Issuance under Equity Compensation Plans

The information required by this item will be included in an amendment to this Annual Report on Form 10-K or incorporated by reference from our definitive proxy statement to be filed pursuant to Regulation 14A within 120 days of the end of the fiscal year covered by this Annual Report on Form 10-K.

Recent Sales of Unregistered Securities

None.

Use of Proceeds from Registered Securities

On June 1, 2021, we completed our IPO and sold 11,500,000 shares of common stock at an IPO price of $16.00 per share. The offer and sale of all of the shares in the IPO were registered under the Securities Act pursuant to registration statements on Form S-1 (File No. 333-255754), which was declared effective by the SEC on May 26, 2021. No additional shares were registered.

We received net proceeds from the IPO of approximately $167.0 million, after deducting underwriting discounts and commissions of approximately $12.9 million and estimated offering expenses of approximately $4.1 million. J.P. Morgan Securities LLC, Cowen and Company, LLC and Piper Sandler & Co. acted as joint book-running managers of the offering and as representatives of the underwriters. None of the expenses associated with the IPO were paid to directors, officers, persons owning 10% or more of any class of equity securities, or to their associates, or to our affiliates.

There has been no material change in the planned use of proceeds from our IPO as described in the prospectus filed with the SEC pursuant to Rule 424(b)(4) under the Securities Act on May 27, 2021.

Purchases of Equity Securities by the Issuer and Affiliated Purchasers

None.

Item 6. Reserved

Item 7. Management's Discussion and Analysis of Financial Condition and Results of Operations.

You should read the following discussion and analysis of our financial condition and results of operations together with our consolidated financial statements and related notes appearing in this Annual Report on Form 10-K. Some of the information contained in this discussion and analysis or set forth elsewhere in this Annual Report on Form 10-K, 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 factors set forth in the "Risk Factors" section of this Annual Report on Form 10-K, our actual results could differ materially from the results described in or implied by the forward-looking statements contained in the following discussion and analysis. For the comparison of the financial results for the fiscal years ended December 31, 2021 and 2020, see Item 7, Management's Discussion and Analysis of Financial Condition and Results of Operations, in our Annual Report on Form 10-K for the fiscal year ended December 31, 2021, filed with the SEC on March 7, 2022. As used in this report, unless the context suggests otherwise, "we," "us," "our," "the Company" or "Day One" refer to Day One Biopharmaceuticals, Inc.

Overview

Day One was founded to address a critical unmet need: children with cancer are being left behind in a cancer drug development revolution. Our name was inspired by the "The Day One Talk" that physicians have with patients and their families about an initial cancer diagnosis and treatment plan. We aim to re-envision cancer drug development and redefine what's possible for all people living with cancer—regardless of age—starting from Day One.

We are a clinical-stage biopharmaceutical company dedicated to developing and commercializing targeted therapies for patients of all ages with life threatening diseases. Initially, we have focused our clinical development efforts on pediatric patients living with cancer, a vulnerable population that has been underserved in the recent revolution in targeted therapeutics and immuno-oncology.

Our lead product candidate, tovorafenib (DAY101), is an oral, brain-penetrant, highly-selective type II pan-rapidly accelerated fibrosarcoma, or pan-RAF, kinase inhibitor. Tovorafenib (DAY101) has been studied in over 325 patients and has been shown to be generally well-tolerated as a monotherapy. Tovorafenib (DAY101) has demonstrated encouraging anti-tumor activity in pediatric and adult populations with specific genetic alterations that result in the over-activation of the RAS/mitogen-activated protein kinase, or MAPK, pathway leading to uncontrolled cell growth.

Tovorafenib (DAY101) has been granted Breakthrough Therapy designation by the FDA in August 2020 for the treatment of pLGG based on initial results from a Phase 1 trial which showed evidence of rapid anti-tumor activity and durable responses in pLGG patients. Pediatric low-grade glioma is the most common brain tumor diagnosed in children for which there is no standard of care and for which there are no approved therapies for the majority of patients. We received Orphan Drug designation for the treatment of malignant glioma from the FDA in September 2020 and from the EU Commission for the treatment of glioma in May 2021. Additionally, the FDA granted Rare Pediatric Disease designation to tovorafenib (DAY101) for treatment of low-grade gliomas, or LGGs, harboring an activating RAF alteration in July 2021.

We have initiated and fully enrolled a pivotal Phase 2 trial, or FIREFLY-1, of tovorafenib (DAY101) as a monotherapy for pediatric patients with relapsed or progressive low-grade glioma harboring an activating BRAF alteration. The first patient was dosed in FIREFLY-1 in May 2021 and we completed enrollment in the registrational arm in May 2022. The FIREFLY-1 trial has also been expanded to: (a) include two additional study arms to enable expanded access for eligible patients now that the primary cohort has completed enrollment, and (b) evaluate the preliminary efficacy of tovorafenib (DAY101) in patients aged six months to 25 years with a relapsed or progressive extracranial solid tumor with an activating RAF fusion. We reported initial data from an interim analysis from the FIREFLY-1 trial in June 2022 and top-line data for all patients in January 2023. Topline data from January 2023 demonstrated an overall response rate, or ORR, of 64% in the 69 Response Assessment for Neuro-Oncology, or RANO, evaluable patients, comprising of 3 confirmed complete responses, or CR, and 41 partial responses, or PR (31 confirmed partial responses and 10 unconfirmed partial response, or uPR). We observed an additional 19 patients with stable disease, or SD, resulting in a clinical benefit rate of 91% (CR+ PR/uPR+ SD). Safety data, based on 77 treated patients, indicated monotherapy tovorafenib to be generally well-tolerated. We

believe tumor reduction or stabilization is clinically meaningful for pLGG patients, as both are perceived as beneficial given the lack of approved therapies for the majority of patients. We anticipate presenting additional data from the FIREFLY-1 trial at an upcoming medical meeting in the second quarter of 2023, and reviewing key portions of the data from the study with the FDA at a pre-New Drug Application, or NDA, meeting in advance of our planned submission of an NDA in the first half of 2023.

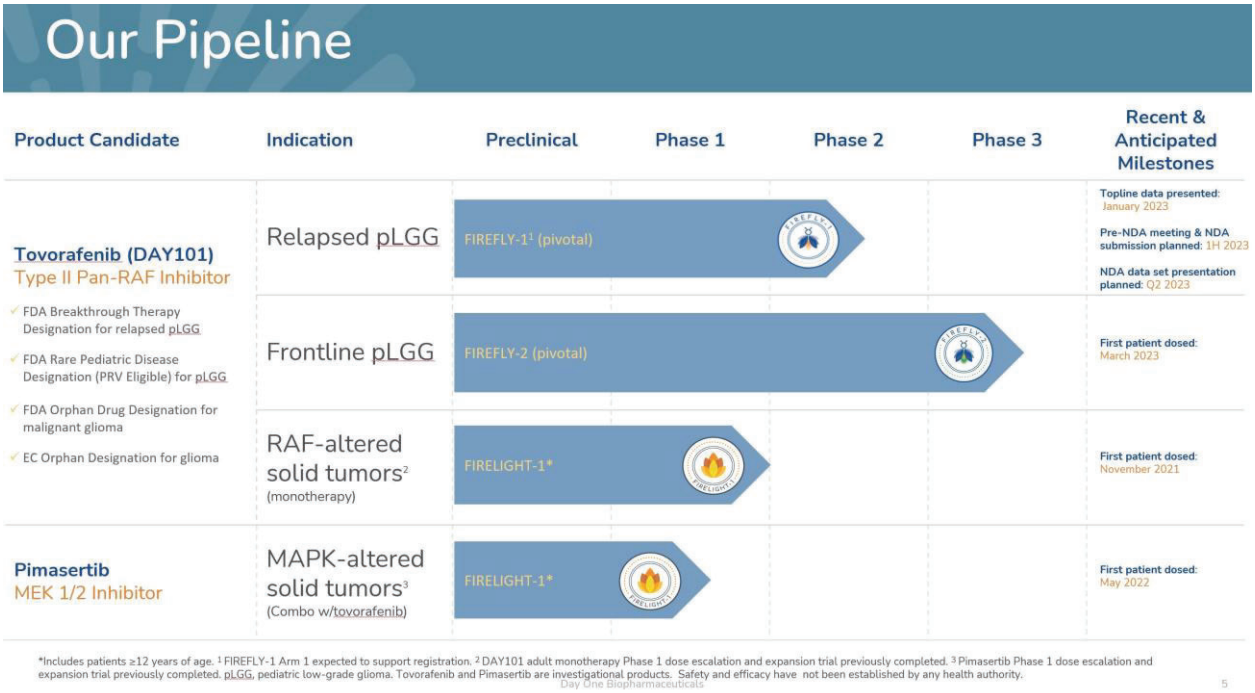
We have initiated a pivotal Phase 3 trial, or FIREFLY-2, of tovorafenib (DAY101) as a frontline therapy in pLGG in the second quarter of 2022, with the first site having been initiated in June 2022. The first patient was dosed in FIREFLY-2 in March 2023.

Our second product candidate, pimasertib, is an oral, highly-selective small molecule inhibitor of mitogen-activated protein kinase kinases 1 and 2, or MEK, a well-characterized key signaling node in the MAPK pathway. Pimasertib has been studied in more than 10 Phase 1/2 clinical trials in over 850 patients with various tumor types, both as monotherapy and in combination with standard of care therapies. Published preclinical studies indicated that pimasertib has higher central nervous system, or CNS, penetration than other MEK inhibitors.

We have initiated an open-label, multicenter, Phase 1b/2a umbrella master trial, or FIRELIGHT-1, of tovorafenib monotherapy or combination therapy, which consists of two substudies. Substudy 1 is a Phase 2 trial of tovorafenib (DAY101) as monotherapy in patients 12 years and older with RAF–altered tumors; the first patient was dosed in November 2021. Substudy 2 is a Phase 1b/2 combination trial of tovorafenib (DAY101) and pimasertib in patients 12 years and older with various MAPK-altered solid tumors; the first patient was dosed in May 2022. Simultaneous inhibition of both RAF and MEK has been shown to lead to synergistic antitumor activity in preclinical models. This combination may demonstrate enhanced anti-tumor activity in a variety of adult solid tumors driven by MAPK alterations, including NRAS mutant melanoma and lung cancers, tumors driven by Class II BRAF alterations, tumors with BRAF wild-type fusions, and tumors driven by KRAS alterations.

We believe our business development capabilities combined with our extensive experience in oncology drug development and deep ties within the research and patient advocacy communities, particularly within the pediatric setting, positions us to be a leader in identifying, acquiring and developing therapies for patients of all ages. We hold exclusive worldwide rights to tovorafenib (DAY101) and to pimasertib for all therapeutic areas subject to certain milestone and royalty payments.

The following table summarizes our product candidate pipeline.



Since our inception in November 2018, we have devoted substantially all of our resources to identifying, acquiring and developing our product candidates and building our pipeline; organizing and staffing our company; business planning; establishing and maintaining our intellectual property portfolio; establishing arrangements with third parties for the manufacture of our product candidates; raising capital; preparing for commercial launch; and providing general and administrative support for these operations. We do not have any products approved for commercial sale and have not generated any revenues from product sales or any other source and have incurred net losses since commencement of our operations. For the years ended December 31, 2022 and 2021, we reported a net loss of $142.2 million and $72.8 million, respectively. We had an accumulated deficit of $269.7 million and $127.5 million as of December 31, 2022 and 2021, respectively. We expect a significant increase in expenses and substantial losses for the foreseeable future as we continue our development of, and seek regulatory approvals for our product candidates, commercialize any approved products, and seek to expand our product pipeline and invest in our organization. In addition, we expect to continue to incur additional costs associated with operating as a public company, including significant legal, audit, accounting, regulatory, tax-related, director and officer insurance, investor relations and other expenses that we did not incur as a private company.

To date, we have funded our operations through the sale of our redeemable convertible preferred shares, convertible notes and common stock in our initial public offering and subsequent public offering.

Cash and cash equivalents and short-term investments totaled $342.3 million as of December 31, 2022. Based on our current operating plan, management believes we have sufficient capital resources to fund anticipated operations into 2025. Because of the numerous risks and uncertainties associated with product development, we may never achieve profitability, and unless and until then, we will need to continue to raise additional capital. There are no assurances that we will be successful in obtaining an adequate level of financing to support our business plans. If we are unable to raise capital as and when needed or on attractive terms, we may have to significantly delay, reduce or discontinue the development and commercialization of our product candidates or scale back or terminate our pursuit of new in-licenses and acquisitions.

We do not own or operate, and currently have no plans to establish, any manufacturing facilities. We rely, and expect to continue to rely, on third parties for the manufacture of our product candidates for clinical testing, as well as for commercial manufacturing if any of our product candidates obtain marketing approval. As we advance our product candidates through development, we will explore adding backup suppliers for the Active Pharmaceutical

Ingredients, or API, drug product, packaging and formulation for each of our product candidates to protect against any potential supply disruptions.

COVID-19 pandemic

The full impact of the ongoing COVID-19 pandemic remains highly uncertain and subject to change. There are many uncertainties around the COVID-19 pandemic and future developments, which are unpredictable, may result in a material, negative impact to our operations and financial condition. We have experienced and expect to continue to experience volatility in services rendered from our third-party service providers as local governments respond to resurgences and the emergence of new strains, each of which may result in the prolonged reinstitution, extension or enhancement of protective measures. With respect to manufacturing and supply, we do not anticipate disruptions to our drug supply chain, and we cannot be sure if lock-down measures or restrictions will be implemented and what, if any, impact that may have on our facilities and operations.

Our management team continues to actively monitor this evolving health crisis and its effects on our financial condition, liquidity, operations, key vendors and workforce.

Inflation Reduction Act

On August 16, 2022, President Biden signed into law the Inflation Reduction Act of 2022, which includes an Alternative Minimum Tax based on the Adjusted Financial Statement Income of Applicable Corporations. Based on our initial evaluation, we do not believe the Inflation Reduction Act will have a material impact on our income tax provision and cash taxes. We continue to monitor the changes in tax laws and regulations to evaluate their potential impact on our business.

Significant Agreements

Takeda asset agreement

On December 16, 2019, DOT Therapeutics-1, Inc., or DOT-1, our subsidiary, entered into an asset purchase agreement, or the Takeda Asset Agreement, with Millennium Pharmaceuticals, Inc., a related party and an affiliate of Takeda Pharmaceutical Company Limited, or Takeda. Pursuant to the Takeda Asset Agreement, DOT-1 purchased certain technology rights and know-how related to TAK-580 (which is now tovorafenib (DAY101)) that provides a new approach for treating patients with primary brain tumors or brain metastases of solid tumors. DOT-1 also received clinical inventory supplies to use in our research and development activities of such RAF-inhibitor and an assigned investigator clinical trial agreement. Takeda also assigned to DOT-1 its exclusive license agreement, or the Viracta License Agreement, with Viracta Therapeutics, Inc. (f/k/a Sunesis Pharmaceuticals, Inc.), or Viracta. Takeda also granted DOT-1 a worldwide, sublicensable exclusive license under specified patents and know-how and non-exclusive license under other patents and know-how generated by Takeda under the Takeda Asset Agreement. DOT-1 also granted Takeda a grant back license, as defined in the Takeda Asset Agreement, which is terminable either automatically or by DOT-1 in the event Takeda does not achieve specified development milestones within the applicable timeframes set forth under the Takeda Asset Agreement. This grant back license to Takeda was terminated at the time of Conversion in connection with the Millennium Stock Exchange Agreement.

In consideration for the sale and assignment of assets and the grant of the license under the Takeda Asset Agreement, DOT-1 made an upfront payment of $1.0 million in cash and issued 9,857,143 shares of Series A redeemable convertible preferred stock in DOT-1 in December 2019. The fair value of issued shares was estimated as $9.9 million, based on the price paid by other investors for issued shares in the Series A financing of DOT-1. Based on the terms of the Millennium Stock Exchange Agreement, Takeda exchanged the 9,857,143 shares of Series A redeemable convertible preferred stock of DOT-1 for 6,470,382 shares of our common stock upon the effectiveness of the Conversion, on May 26, 2021.

The term of the Takeda Asset Agreement will expire on a country-by-country basis upon expiration of all assigned patent rights and all licensed patent rights in such country. Takeda may terminate the Takeda Asset Agreement prior to our first commercial sale of a product if we cease conducting any development activities for a continuous and specified period of time and such cessation is not agreed upon by the parties and is not done in response to guidance from a regulatory authority. Additionally, Takeda can terminate the Takeda Asset Agreement in the event of our bankruptcy. In the event of termination of the Takeda Asset Agreement by Takeda as a result of our cessation of development or bankruptcy, all assigned patents, know-how and contracts (other than the Viracta License Agreement) will be assigned back to Takeda and Takeda will obtain a reversion license under patents and know-how generated to exploit all such terminated products.

Effective December 31, 2021, DOT-1 was merged with and into our company, with our company being the surviving corporation and assuming DOT-1's obligations under the Takeda Assets Purchase Agreement.

Viracta license agreement

On December 16, 2019, DOT-1 amended and restated the Viracta License Agreement that was assigned pursuant to the Takeda Asset Agreement. Under the Viracta License Agreement, DOT-1 received a worldwide exclusive license under specified patent rights and know-how to develop, use, manufacture, and commercialize products containing compounds binding the RAF protein family.

DOT-1 paid $2.0 million upfront in cash to Viracta, which was recorded as research and development expenses in 2019. DOT-1 made a milestone payment of $3.0 million to Viracta in February 2021, which was recorded as research and development expense when the milestone was achieved in April 2021. DOT-1 is also required to make additional milestone payments of up to $54.0 million upon achievement of specified development and regulatory milestones for each licensed product in two indications, with milestones payable for the second indication to achieve a specified milestone event being lower than milestones payable for the first indication. Additionally, if DOT-1 obtains a priority review voucher with respect to a licensed product and sells such priority review voucher to a third party or uses such priority review voucher, DOT-1 is obligated to pay Viracta a specified percentage in the mid-teen digits of all net consideration received from any such sale or of the value of such used priority review voucher, as applicable. Commencing on the first commercial sale of a licensed product in a country, DOT-1 is obligated to pay tiered royalties ranging in the mid-single-digit percentages on net sales of licensed products, if any. The obligation to pay royalties will end on a country-by-country and licensed product-by-licensed product basis commencing on the first commercial sale in a country and continuing until the later of: (i) the expiration of the last valid claim of the Viracta licensed patents, jointly owned collaboration patents or specified patents owned by the Company covering the use or sale of such product in such country, (ii) the expiration of the last statutory exclusivity pertaining to such product in such country or (iii) the tenth anniversary of the first commercial sale of such product in such country. No other milestones, except as discussed above, were achieved and due as of December 31, 2022.

The term of the Viracta License Agreement will expire on a licensed product-by-licensed product and country-by-country basis upon the expiration of the Company's obligation to pay royalties to Viracta with respect to such product in such country. DOT-1 has the right to terminate the Viracta License Agreement with respect to any or all of the licensed products at will upon a specified notice period.

Effective December 31, 2021, DOT-1 was merged with and into our company, with our company being the surviving corporation and assuming DOT-1's obligations under Viracta License Agreement.

License agreement with Merck KGaA, Darmstadt, Germany

On February 10, 2021, DOT Therapeutics-2, Inc., or DOT-2, our subsidiary, entered into a license agreement, or the MRKDG License Agreement, with Merck KGaA, Darmstadt, Germany, a pharmaceutical corporation located in Darmstadt, Germany. Under the MRKDG License Agreement, Merck KGaA, Darmstadt, Germany granted to us an exclusive worldwide license, with the right to grant sublicenses through multiple tiers, under specified patent rights and know-how for us to research, develop, manufacture and commercialize products containing and comprising the pimasertib and MSC2015103B compounds. We also received clinical inventory supplies to use in its

research and development activities. Our exclusive license grant is subject to a non-exclusive license granted by Merck KGaA, Darmstadt, Germany's affiliate to a cancer research organization and Merck KGaA, Darmstadt, Germany retains the right to conduct, directly or indirectly, certain ongoing clinical studies relating to pimasertib.

Under the MRKDG License Agreement, we have obligations to use commercially reasonable efforts to develop and commercialize at least two licensed products in at least two specified major market countries by the year 2029.

In consideration for the rights granted under the MRKDG License Agreement and clinical supplies, we made an upfront payment of $8.0 million, which was recorded as research and development expenses, as the technology does not have an alternative future use and supplies are used for research activities. Additionally, we made a milestone payment of $2.5 million, which was recorded as research and development expenses due to the nature of the license agreement and the milestone event relating to the first dosing of a patient in a first clinical trial of a product containing pimasertib, in the year ended December 31, 2022. We may also be required to make additional payments of up to $364.5 million based upon the achievement of specified development, regulatory, and commercial milestones, as well a high, single-digit royalty percentage on future net sales of licensed products, if any. Milestones and royalties are contingent upon future events and will be recorded when the milestones are achieved and when payments are due.

The term of the MRKDG License Agreement will expire on a licensed product-by-licensed product and country-by-country basis upon the expiration of our obligation to pay royalties to the licensor with respect to such licensed product in such country and will expire in its entirety upon the expiration of all of our payment obligations with respect to all licensed products and all countries under the MRKDG License Agreement.

Effective December 31, 2021, DOT-2 was merged with and into our company, with our company being the surviving corporation and assuming DOT-2's obligations under the MRKDG License Agreement.

Components of Results of Operations

Operating expenses

Research and development expenses

Research and development expenses consist primarily of external and internal expenses incurred for our research activities, including our discovery and in-licensing undertakings, and the development of our lead product candidate, tovorafenib (DAY101) and our second product candidate, pimasertib.

External expenses include:

- costs associated with acquiring technology and intellectual property licenses that have no alternative future uses;
- costs incurred under agreements with third-party contract research organizations, or CROs, contract manufacturing organizations, or CMOs, and other third parties that conduct clinical trials on our behalf; and
- other costs associated with our research and development programs, including laboratory materials and supplies.

Internal expenses include:

- employee-related costs, including salaries, benefits and share-based compensation expense, for our research and development personnel; and
- facilities and other overhead expenses, including expenses for rent and facilities maintenance, and amortization.

We expense research and development expenses as incurred. We track external costs by program, which currently consist of expenses for our tovorafenib (DAY101) program and our pimasertib program. We do not track indirect costs on a program specific basis because these costs are deployed across multiple programs and, as such, are not separately classified.

Research and development activities are central to our business model. We expect that our research and development expenses will increase substantially for the foreseeable future as we continue to implement our business strategy, advance tovorafenib (DAY101) and pimasertib through clinical trials and conduct larger clinical trials, expand our research and development efforts, and identify, acquire and develop additional product candidates, particularly as more of our product candidates move into clinical development and later stages of clinical development.

We cannot reasonably determine the duration and costs to complete future clinical trials of tovorafenib (DAY101), pimasertib or any other product candidate we may develop or acquire, or to what extent we will generate revenue from the commercialization and sale of any of our product candidates. The successful development and commercialization of our product candidates, as well as our ability to obtain the necessary regulatory and marketing approvals are highly uncertain. This is due to numerous risks and uncertainties associated with developing new drugs, many of which are outside of our control, including:

- the scope, rate of progress, expense and results of preclinical development activities, as well as of any future clinical trials of our product candidates, and other 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 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, European Medicines Agency, Health Canada or other regulatory agencies of the investigational NDAs, clinical trial applications or other regulatory filings for tovorafenib (DAY101) and future product candidates;
- obtaining and maintaining intellectual property protection and regulatory exclusivity for our product candidates;
- 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;
- retention and expansion of a workforce of experienced scientists and others to continue research and development of our product candidates;
- maintaining a continued acceptable safety profile of the products following any marketing approvals.
- significant and changing government regulation and regulatory guidance;
- the impact of any business interruptions to our operations or to those of the third parties with whom we work, including due to the ongoing COVID-19 pandemic; and

- the extent to which we establish additional strategic collaborations or other arrangements.

A change in estimates of any of these factors could mean a significant change in the costs and timing associated with the development of our current and future product candidates. For example, if the FDA or another regulatory authority were to require us to conduct clinical trials beyond those that we currently anticipate will be required for the completion of clinical development of a product candidate, or if we experience significant delays in our ongoing and planned clinical trials due to patient enrollment or other reasons, we could be required to expend significant additional financial resources and time on the completion of clinical development.

General and administrative expenses

General and administrative expenses consist primarily of personnel-related costs, legal and professional service costs, insurance costs and facility-related costs. Personnel-related costs include salaries, bonuses, benefits, share-based compensation, travel expenses and other related costs, for personnel in our executive, finance, corporate, business development, and administrative functions. Legal and professional service expenses include legal fees related to intellectual property and corporate matters; professional fees for accounting, auditing, tax, human resources, business development, and other consulting services; and travel expenses and facilities-related expenses.

We expect that our general and administrative expenses will increase substantially for the foreseeable future as we anticipate an increase in our personnel headcount to support expansion of research and development efforts for our product candidates, increase our team and resources dedicated to commercial market preparation, as well as to support our operations generally. We also expect an increase in expenses associated with being a public company, including costs related to compliance with the requirements of the Nasdaq Global Select Market, or Nasdaq, and the Securities and Exchange Commission, or SEC; additional director and officer insurance costs; and investor and public relations costs.

Net loss attributable to redeemable convertible noncontrolling interest

Net loss attributable to redeemable convertible noncontrolling interest represented a portion of the net loss that is not allocated to us in our subsidiary, DOT-1. On May 26, 2021, in connection with the terms of the Millennium Stock Exchange Agreement, Takeda exchanged its shares in DOT-1 for shares of our common stock. At that time, the redeemable convertible noncontrolling interest was extinguished, and DOT-1 became our wholly owned subsidiary.

Exchange of redeemable noncontrolling interest shares – deemed dividend

For the year ended December 31, 2021, as a result of an exchange of shares by Takeda, we recognized an extinguishment loss of approximately $100.0 million to additional paid-in-capital, which was calculated as a difference between the fair value of common stock issued to Takeda in the conversion and the carrying value of redeemable noncontrolling interest at the conversion date. The all-stock, non-cash exchange was treated as a deemed dividend in the calculation of net loss attributable to common stockholders and net loss per share.

Results of Operations

Comparison of year ended December 31, 2022 and 2021

The following table summarizes our results of operations for the years ended December 31, 2022 and 2021:

	Year Ended December 31,			
	2022	2021	$ Change	% Change
Operating expenses:				
Research and development	$ 85,618	$ 43,584	$ 42,034	96.4%
General and administrative	61,291	29,159	32,132	110.2%
Total operating expenses	146,909	72,743	74,166	102.0%
Loss from operations	(146,909)	(72,743)	(74,166)	102.0%
Interest income, net	4,746	4	4,742	*
Other expense, net	(18)	(15)	(3)	20.0%
Net loss	(142,181)	(72,754)	(69,427)	95.4%
Net loss attributable to redeemable convertible noncontrolling interests	—	(2,109)	2,109	*
Exchange of redeemable noncontrolling interest shares – deemed dividend	—	(99,994)	99,994	*
Net Loss attributable to common stockholders/members	$ (142,181)	$ (170,639)	$ 28,458	-16.7%

Research and development expenses

Research and development expenses increased $42.0 million, from $43.6 million for the year ended December 31, 2021, to $85.6 million for the year ended December 31, 2022. In the year ended December 31, 2022, as compared to December 31, 2021, third-party expenses increased by $29.0 million, due primarily to an increase in clinical trial, manufacturing and other product development expenses, personnel related expenses increased by $18.1 million resulting from additional headcount and share-based compensation, and upfront and milestone expenses decreased by $8.5 million due to the timing of milestone payments.

The following table summarizes our external and internal research and development expenses for the years ended December 31, 2022 and 2021:

	Year Ended December 31,	
	2022	2021
	(in thousands)	
External costs:		
Third-party CRO, CMO and other third-party clinical trial costs (1)	$ 50,175	$ 21,181
Milestone payment related to the MRKDG License Agreement	2,500	—
Upfront payment related to the MRKDG License Agreement	—	8,000
Milestone payment related to the Viracta License Agreement	—	3,000
Other research and development costs, including laboratory materials and supplies	3,598	243
Internal costs:		
Employee related expenses	29,345	11,160
Total research and development expenses	$ 85,618	$ 43,584

(1) Third-party CRO, CMO and other clinical trial costs for the tovorafenib (DAY 101) program and the pimasertib program were $43.2 million and $6.9 million, respectively, for year ended December 31, 2022, compared to $19.8 million and $1.4 million, respectively, for the year ended December 31, 2021.

General and administrative expenses

General and administrative expenses increased $32.1 million, from $29.2 million for the year ended December 31, 2021 to $61.3 million for the year ended December 31, 2022. The increase in general and administrative expenses was primarily due to $17.1 million in employee compensation costs driven by headcount growth, $10.6 million in professional services, legal and insurance driven by the build out of commercial capabilities and continued expansion of business operations and $4.4 million in facilities costs and other expenses.

Exchange of redeemable noncontrolling interest shares – deemed dividend

In May 2021, we exchanged Takeda's redeemable noncontrolling interest shares in DOT-1 for shares of common stock of Day One Biopharmaceuticals, Inc., which resulted in accounting for the transaction as a deemed dividend. As such, we recognized a $100.0 million non-cash extinguishment loss to additional paid-in capital, which was calculated as a difference between the fair value of common stock issued to Takeda in the Conversion and the carrying value of the redeemable noncontrolling interest at the conversion date. This was disclosed below net loss on the consolidated statements of operations as a deemed dividend and included in the net loss per share calculation for the year ended December 31, 2021. There was no such loss recognized during the year ended December 31, 2022.

Liquidity and Capital Resources

Sources of liquidity

In June 2022, we entered into an equity distribution agreement with Piper Sandler & Co. and JonesTrading Institutional Services LLC, as sales agents, relating to the issuance and sale of shares of our common stock having an aggregate offering price of up to $150.0 million from time to time, or the 2022 ATM. The issuance and sale of these shares by us pursuant to the 2022 ATM were deemed an "at-the-market" offering under the Securities Act. As of December 31, 2022, we have not sold any shares of our common stock under the 2022 ATM.

In June 2022, we completed a follow-on offering and issued and sold 11,500,000 shares of common stock (including the exercise by the underwriters of their option to purchase an additional 1,500,000 shares of common stock) at a price to the public of $15.00 per share for net proceeds of approximately $161.6 million, after deducting underwriting discounts, commissions and offering costs.

In June 2021, we completed our IPO and sold an aggregate of 11,500,000 shares of common stock at a price to the public of $16.00 per share, which included 1,500,000 shares issued upon the full exercise by the underwriters in May 2021 of their option to purchase additional shares of common stock. We received aggregate net proceeds from the IPO of $167.0 million, after deducting underwriting discounts, commissions, and offering costs of $17.0 million. Prior to our IPO, we had funded our operations through the sale of our redeemable convertible preferred shares and convertible notes. We had previously raised approximately $192.0 million in gross proceeds from the sale and issuance of our Series A and Series B redeemable convertible preferred shares and convertible notes.

As of December 31, 2022, we had an accumulated deficit of $269.7 million and $342.3 million in cash, cash equivalents and short-term investments. We believe our cash, cash equivalents and short-term investments will be sufficient to satisfy our cash requirements over the next 12 months and into 2025.

Our primary use of cash is to fund operating expenses, which consist primarily of research and development expenditures including our license, clinical trial and laboratory costs as well as to a lesser extent, general and administrative expenditures including our salary and consulting expenses. Cash used to fund operating expenses is impacted by the timing of when we pay these expenses, as reflected in the change in our outstanding accounts payable and accrued expenses. Our material cash requirements include the following contractual and other obligations.

Leases

We have an operating lease obligation for office space. As of December 31, 2022, the Company had fixed lease payment obligations of approximately $0.9 million, with approximately $0.5 million payable within 12 months.

Contract Research Organizations and Contract Manufacturing Organizations

We have entered into contracts in the normal course of business with CROs, CMOs, and other third-party vendors for clinical trial, manufacturing, testing, and other research and development activities. These contracts generally provide for termination on notice, with the exception of one vendor where certain costs are non-cancellable after the approval of the project. As of December 31, 2022, there were no amounts accrued related to termination and cancellation charges as these are not probable.

License Agreements

We have entered into licensing agreements, which require us to pay milestones contingent upon meeting of specific events. We made milestones payment of $2.5 million related to the first dosing of a patient in a first clinical trial of a product containing pimasertib in the year ended December 31, 2022 and $3.0 million related to the Viracta License Agreement in the year ended December 31, 2021. We are required to pay royalties on sales of products developed under these agreements. All our products are in development as of December 31, 2022 and no such royalties are due. As of December 31, 2022, we do not have any contingent payment obligations since the amount, timing and likelihood of such payments are not known.

Cash flows

The following table summarizes our sources and uses of cash for the periods presented:

	Year Ended December 31,	
	2022	2021
Net cash used in operating activities	$ (109,874)	$ (48,539)
Net cash used in investing activities	(255,074)	(8,000)
Net cash provided by financing activities	165,901	297,120
Net (decrease) increase in cash and cash equivalents	$ (199,047)	$ 240,581

Operating activities

Net cash used in operating activities for the year ended December 31, 2022 was $109.9 million, consisting of our net loss of $142.2 million, changes of approximately $6.6 million in net operating assets and liabilities and by non-cash charges of $25.7 million, which is primarily comprised of share-based compensation expense of $27.2 million. Changes in operating assets and liabilities were primarily related to an increase in accrued expenses and other current liabilities of $9.2 million. This was partially offset by a decrease of accounts payable of $1.5 million, an increase to operating lease liabilities of $0.3 million, an increase to deposits and other long-term assets of $0.3 million, and an increase to prepaid expenses and other current assets of $0.5 million.

Net cash used in operating activities for the year ended December 31, 2021 was $48.5 million, consisting of our net loss of $72.8 million, partially offset by $2.7 million in net operating assets and liabilities and by non-cash charges of $21.5 million. Changes in operating assets and liabilities were primarily related to an increase in prepaid expenses and other current assets of $3.7 million, which includes $3.0 million prepayment of the Viracta license milestone, partially offset by an increase in accrued expenses and other current liabilities of $5.1 million, and an increase in accounts payable of $1.5 million. Our non-cash charges primarily consisted of $13.3 million in share-based compensation expense and $0.2 million in non-cash lease expense. We also paid $8.0 million related to the MRKDG License Agreement, which was recognized as research and development expenses and presented in investing activities in our consolidated statements of cash flows.

Investing activities

Net cash used in invested activities for the year ended December 31, 2022 was $255.1 million attributable to the purchase of short-term investments and property and equipment expenditures of $0.4 million. This was partially offset by the proceeds from the maturity of short-term investments of $0.1 million.

Net cash used in investing activities for the year ended December 31, 2021 was $8.0 million, attributable to the payment under the MRKDG License Agreement.

Financing activities

Net cash provided by financing activities for the year ended December 31, 2022 was $165.9 million, primarily attributable to the net proceeds from the issuance of common stock in connection with our follow-on offering of common stock. Additionally, there was $4.3 million of net cash provided by financing activities related to proceeds from the issuance of common stock upon stock option exercises and purchases made under our 2021 Employee Stock Purchase Plan.

Net cash provided by financing activities for the year ended December 31, 2021 was $297.1 million, attributable to $167.0 million related to the net proceeds from the issuance of common stock in connection with the IPO, and $129.8 million related to the net proceeds from the sale and issuance of Series B redeemable convertible preferred shares.

Funding requirements

Since our inception, we have incurred significant operating losses. We expect to continue to incur significant expenses and increasing operating losses for the foreseeable future in connection with our ongoing activities.

We believe our existing cash, cash equivalents and short-term investments will enable us to fund our operating expenses and capital expenditure requirements into 2025. We have based this estimate on assumptions that may prove to be imprecise, and we could use our available capital resources sooner than we currently expect.

As a result of anticipated expenditures, we will need to obtain substantial additional financing in connection with our continuing operations. Until such time, if ever, as we cannot generate substantial revenue from product sales, we expect to finance our cash needs through a combination of equity offerings, debt financings, collaborations, strategic alliances and marketing, distribution or licensing arrangements. Adequate additional funds may not be available to us on acceptable terms, or at all. If we are unable to raise capital when needed or on attractive terms, we may be required to delay, limit, reduce or terminate our research, product development programs or any future commercialization efforts or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

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 a common stockholder. Debt financing and preferred equity financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making acquisitions or capital expenditures or declaring dividends.

If we raise additional funds through collaborations, strategic alliances or marketing, distribution 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.

Our ability to raise additional funds may be adversely impacted by potential worsening global economic conditions, including inflation and changing interest rates, and disruptions to and volatility in the credit and financial markets in the United States and worldwide resulting from the ongoing COVID-19 pandemic or otherwise. Because of the numerous risks and uncertainties associated with product development, we cannot predict the timing or amount of increased expenses and cannot assure you that we will ever be profitable or generate positive cash flow from operating activities.

Off-balance sheet arrangements

We did not during the periods presented, and we do not currently have, any off-balance sheet arrangements, as defined in the rules and regulations of the SEC other than our indemnification agreements as described in Note 6 of our consolidated financial statements included elsewhere in this Annual Report on Form 10-K.

Critical Accounting Policies and Use of Estimates

Our management's discussion and analysis of financial condition and results of operations is based on our consolidated financial statements, which have been prepared in accordance with generally accepted accounting principles in the United States, or GAAP. The preparation of consolidated financial statements in conformity with GAAP requires management to make estimates and assumptions that affect the reported amounts of assets, liabilities and disclosure of contingent assets and liabilities at the date of the consolidated financial statements and the reported amounts of expenses during the reporting period. We base our estimates on historical experience, known trends and events and various other factors that we believe are reasonable under the circumstances, the results of which form the basis for making judgments about the carrying values of assets and liabilities that are not readily apparent from other sources. We evaluate our estimates and assumptions on an ongoing basis. Our actual results may differ from these estimates under different assumptions or conditions.

While our significant accounting policies are described in more detail in the Notes to our Consolidated Financial Statements appearing within Item 8 of this Annual Report, we believe that the following accounting policies are those most critical to the judgments and estimates used in the preparation of our consolidated financial statements.

Accrued research and development expenses

We record accrued liabilities for estimated costs of our research and development activities conducted by third-party service providers, which include the conduct of preclinical and clinical studies and contract manufacturing activities. We record the estimated costs of research and development activities based upon the estimated amount of services provided but not yet invoiced. We accrue for these costs based on factors such as estimates of the work completed and in accordance with agreements established with our third-party service providers under the service agreements.

We make payments in connection with clinical trials under contracts with CMOs and CROs that support conducting and managing our clinical trials. The financial terms of these contracts are subject to negotiation, which vary by contract and may result in payments that do not match the periods over which materials or services are provided. Generally, these agreements set forth the scope of work to be performed at a fixed fee, unit price or on a time and materials basis. We accrue costs for clinical trial activities performed by CROs based upon the estimated amount of work completed on each trial. For clinical trial expenses, the significant factors used in estimating accruals include the number of patients enrolled, the activities to be performed for each patient, the number of active clinical sites and the duration for which the patients will be enrolled in the trial. We monitor patient enrollment levels and related activities to the extent possible through internal reviews, correspondence with CROs and review of contractual terms. We base our estimates on the best information available at the time. In accruing service fees of CMOs, we estimate the time period over which services will be performed and the level of effort to be expended in each period. Clinical supplies inventories that have no alternative use are recorded to research and development expense as ownership for these supplies passes to us.

If we do not identify costs that have begun to be incurred or if we under- or over-estimate the level of services performed or the costs of these services, actual expenses could differ from our estimates. To date, we have not experienced any material differences between accrued costs and actual costs incurred. However, due to the nature of estimates, we cannot assure that we will not make changes to our estimates in the future as we become aware of additional information about the status or conduct of our clinical trials and other research activities.

Share-based compensation

Prior to our IPO, we recognized share-based compensation expense based on the estimated fair value of all share-based awards, incentive shares and restricted share awards, on the date of grant using the option-pricing model. The option-pricing model requires the input of subjective assumptions, including the fair value of the underlying common shares, the expected term of the award, the expected volatility, risk-free interest rates and the dividend yield. In determining the fair value of common shares, the methodologies used to estimate the enterprise value were performed using methodologies, approaches and assumptions consistent with the American Institute of Certified Public Accountants Accounting and Valuation Guide, Valuation of Privately-Held-Company Equity Securities Issued as Compensation. The participation threshold amounts were determined by the board of directors at the time of grant. The expected life of the awards granted during the period was determined based on an expected time to the liquidation event. We applied the risk-free interest rate based on the U.S. Treasury yield in effect at the time of the grant consistent with the life of the award. The expected volatility was based on a peer group in the

industry in which we did business consistent with the expected time to liquidity. The dividend yield was set at zero as the underlying security did not and was not expected to pay a dividend.

Subsequent to closing of the IPO, we use the Black-Scholes valuation model to estimate the fair value of options granted, intrinsic value to estimate the fair value of restricted stock awards, and fair value of our common stock at the grant date for restricted stock units.

The Black-Scholes option-pricing model, used to estimate fair value of stock options awards, requires the use of the following assumptions:

- *Fair Value of Common Stock*—the closing price on the Nasdaq market at the grant date.

- *Expected Term*—The expected term represents the period that the share-based awards are expected to be outstanding. The expected term for stock options is calculated using the simplified method, as the weighted-average vesting term of the award and the award's contract period. We utilize this method due to lack of historical exercise data and the plain-vanilla nature of our service condition share-based awards. For our performance condition stock option awards, we calculate the expected term by taking into consideration the option's contractual life, the timing of when milestones are expected to be achieved and the expected exercise period by a holder from the vesting date until the contractual term.

- *Expected Volatility*—Since we do not have sufficient trading history for our common stock, the expected volatility is estimated based on the average historical volatilities of common stock of comparable publicly traded biopharmaceutical companies over a period equal to the expected term of the stock option grants. The comparable biopharmaceutical companies are chosen based on their size, stage in the life cycle or area of specialty. We will continue to apply this process until sufficient historical information regarding the volatility of the common stock price becomes available.

- *Risk-Free Interest Rate*—The risk-free interest rate is based on the U.S. Treasury yield in effect at the time of grant for zero-coupon U.S. Treasury notes with maturities approximately equal to the expected term of the awards.

- *Expected Dividend Yield*—We have never paid dividends on the common stock and have no plans to pay dividends on our common stock. Therefore, the expected dividend yield used is zero.

We recognize forfeitures by reducing the expense in the same period the forfeitures occur. We recognize share-based compensation expense for awards with performance conditions when it is probable that the condition will be met, and the award will vest.

The assumptions underlying these valuations represented management's best estimates, which involved inherent uncertainties and the application of management's judgment. As a result, if we had used significantly different assumptions or estimates, the fair value of our common stock and our share-based compensation expense could have been materially different.

New Accounting Pronouncements

Refer to Note 2 of the Notes to our Consolidated Financial Statements included elsewhere in this Annual Report on Form 10-K for a summary of recently issued and adopted accounting pronouncements.

Emerging Growth Company Status

As an emerging growth company, or EGC, under the Jumpstart Our Business Startups Act of 2012, or JOBS Act, we can take advantage of an extended transition period for complying with new or revised accounting standards. This provision allows an EGC to delay the adoption of some accounting standards until those standards would otherwise apply to private companies. We have elected to use this extended transition period for complying

with new or revised accounting standards that have different effective dates for public and private companies until the earlier of the date we (i) are no longer an emerging growth company or (ii) affirmatively and irrevocably opt out of the extended transition period provided in the JOBS Act. As of December 31, 2023, we will lose our status as an emerging growth company and will no longer be able to take advantage of the exemptions from various reporting requirements beginning with our annual report for the fiscal year ending December 31, 2023 to be filed in 2024.

Item 7A. Quantitative and Qualitative Disclosures About Market Risk.

We are a smaller reporting company as defined by Rule 12b-2 of the Exchange Act and are not required to provide the information required under this item.

Item 8. Financial Statements and Supplementary Data.

The information required by this Item is set forth in the consolidated financial statements and notes thereto beginning at page F-1 of this Annual Report on Form 10-K.

Item 9. Changes in and Disagreements with Accountants on Accounting and Financial Disclosure.

None.

Item 9A. Controls and Procedures.

Evaluation of Disclosure Controls and Procedures

As of December 31, 2022, management, with the participation of our Principal Executive Officer and Principal Financial and Accounting Officer, performed an evaluation of the effectiveness of our disclosure controls and procedures as defined in Rules 13a-15(e) and 15d-15(e) of the Securities Exchange Act of 1934, as amended, or the Exchange Act. Our disclosure controls and procedures are designed to ensure that information required to be disclosed in the reports we file or submit under the Exchange Act is recorded, processed, summarized, and reported within the time periods specified in the SEC's rules and forms, and that such information is accumulated and communicated to our management, including the Principal Executive Officer and the Principal Financial and Accounting Officer, to allow timely decisions regarding required disclosures. Any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving the desired control objective and management necessarily applies its judgment in evaluating the cost-benefit relationship of possible controls and procedures. Based on this evaluation, our Principal Executive Officer and Principal Financial and Accounting Officer concluded that, as of December 31, 2022, our disclosure controls and procedures were effective at a reasonable assurance level.

Management's Report on Internal Control Over Financial Reporting

Our management is responsible for establishing and maintaining adequate internal control over financial reporting. Internal control over financial reporting is defined in Rules 13a-15(f) and 15d-15(f) promulgated under the Exchange Act as a process designed by, or under the supervision of, our chief executive officer and chief financial officer and effected by our board of directors, management and other personnel to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with U.S. GAAP. Our internal control over financial reporting includes those policies and procedures that:

- pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect our transactions and dispositions of our assets;

- provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with U.S. GAAP, and that our receipts and expenditures are being made only in accordance with authorizations of our management and directors; and

- provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use or disposition of our 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. Therefore, even those systems determined to be effective can provide only reasonable assurance with respect to financial statement preparation and presentation. 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. Additionally, in designing disclosure controls and procedures, our management necessarily was required to apply its judgment in evaluating the cost-benefit relationship of possible disclosure controls and procedures. The design of any disclosure controls and procedures 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.

Our management, with the participation of our chief executive officer and chief financial officer, assessed the effectiveness of our internal control over financial reporting as of December 31, 2022. In making this assessment, management used the criteria set forth by the Committee of Sponsoring Organizations of the Treadway Commission (COSO) in its Internal Control – Integrated Framework (2013). Based on our assessment, our management has concluded that, as of December 31, 2022, our internal control over financial reporting is effective based on those criteria.

This Annual Report on Form 10-K does not include an attestation report of our independent registered public accounting firm regarding internal control over financial reporting. For as long as we remain an "emerging growth company" as defined in Section 2(a) of the Securities Act of 1933, as amended, or the Securities Act, as modified by the Jumpstart Our Business Startups Act of 2012, we intend to take advantage of the exemption permitting us not to comply with the requirement that our independent registered public accounting firm provide an attestation on the effectiveness of our internal control over financial reporting.

Changes in Internal Control over Financial Reporting

There were no changes in our internal control over financial reporting that occurred during the most recent quarter that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

Item 9B. Other Information.

None.

Item 9C. Disclosure Regarding Foreign Jurisdictions that Prevent Inspections.

None.

PART III

Item 10. Directors, Executive Officers and Corporate Governance.

The information required by this Item is incorporated herein by reference to the sections titled "Information about our Executive Officers," "Election of Directors," "Corporate Governance" and "Security Ownership of Certain Beneficial Owners and Management" in our Definitive Proxy Statement with respect to our 2023 Annual Meeting of Stockholders to be filed with the SEC within 120 days after the end of the fiscal year covered by this Annual Report on Form 10-K.

With regard to the information required by this item regarding compliance with Section 16(a) of the Exchange Act, we will provide disclosure of delinquent Section 16(a) reports, if any, in our Proxy Statement related to the 2023 Annual Meeting of Shareholders, and such disclosure, if any, is incorporated herein by reference.

We have adopted a Code of Business Conduct and Ethics that applies to all of our officers, directors, and employees, including our principal executive officer, principal financial officer, principal accounting officer, and controller, or persons performing similar functions, which is posted on our website. Our Code of Business Conduct and Ethics is a "code of ethics," as defined in Item 406(b) of Regulation S-K. We will make any legally required disclosures regarding amendments to, or waivers of, provisions of our Code of Business Conduct and Ethics on our website. The information contained on, or accessible from, our website is not part of this Annual Report on Form 10-K by reference or otherwise.

Item 11. Executive Compensation.

The information required by this Item is incorporated herein by reference to the sections titled "Executive Compensation," "Election of Directors," and "Corporate Governance" in our Definitive Proxy Statement with respect to our 2023 Annual Meeting of Stockholders to be filed with the SEC within 120 days after the end of the fiscal year covered by this Annual Report on Form 10-K.

Item 12. Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters.

The information required by this Item is incorporated herein by reference to the sections titled "Security Ownership of Certain Beneficial Owners and Management" and "Equity Compensation Plan Information" in our Definitive Proxy Statement with respect to our 2023 Annual Meeting of Stockholders to be filed with the SEC within 120 days after the end of the fiscal year covered by this Annual Report on Form 10-K.

Item 13. Certain Relationships and Related Transactions, and Director Independence.

The information required by this Item is incorporated herein by reference to the sections titled "Certain Relationships and Related Party Transactions" and "Corporate Governance" in our Definitive Proxy Statement with respect to our 2023 Annual Meeting of Stockholders to be filed with the SEC within 120 days after the end of the fiscal year covered by this Annual Report on Form 10-K.

Item 14. Principal Accounting Fees and Services.

The information required by this Item is incorporated herein by reference to the section titled "Ratification of Independent Registered Public Accounting Firm" in our Definitive Proxy Statement with respect to our 2023 Annual Meeting of Stockholders to be filed with the SEC within 120 days after the end of the fiscal year covered by this Annual Report on Form 10-K.

PART IV

Item 15. Exhibits, Financial Statement Schedules.

(1) Consolidated Financial Statements:

The consolidated financial statements required by Item 15(a) are filed as part of this Annual Report on Form 10-K under Item 8 "Consolidated Financial Statements and Supplementary Data."

(2) Consolidated Financial Statement Schedules

The financial statement schedules required by Item 15(a) are omitted because they are not applicable, not required or the required information is included in the consolidated financial statements or notes thereto as filed in Item 8 of this Annual Report on Form 10-K.

(3) Exhibits.

Exhibit Number	Description	Form	File No.	Exhibit Filing Date	Filed/ Furnished Herewith
3.1	Restated Certificate of Incorporation, dated June 1, 2021.	10-Q	001-40431	August 10, 2021	
3.2	Amended and Restated Bylaws, dated February 17, 2023.	8-K	001-40431	February 23, 2023	
3.3	Certificate of Ownership and Merger, dated December 23, 2021	10-K	001-40431	March 7, 2022	
4.1	Form of Common Stock Certificate	S-1/A	333-255754	May 24, 2021	
4.2	Amended and Restated Investors' Rights Agreement, dated February 1, 2021, by and among Day One Biopharmaceuticals Holding Company, LLC and certain of its stockholders.	S-1	333-255754	May 4, 2021	
4.3	Description of Registrant's Securities	10-K	001-40431	March 7, 2022	
10.1^	Form of Indemnification Agreement with directors and officers	S-1	333-255754	May 4, 2021	
10.2^	Form of Change in Control and Severance Agreement	10-K	001-40431	March 7, 2022	
10.3^	2021 Equity Incentive Plan and forms of award agreements	S-1	333-255754	May 4, 2021	
10.4^	2021 Employee Stock Purchase Plan and forms of award agreements thereunder	S-1	333-255754	May 4, 2021	

10.5†	Office Lease, dated April 1, 2022, by and between Aircraft Technical Publishers, a California corporation, and Day One Biopharmaceuticals, Inc.	10-Q	001-40431	August 4, 2022	
10.6†	Asset Transfer and License Agreement, effective as of December 16, 2019, by and between DOT Therapeutics-1, Inc. and Millennium Pharmaceuticals, Inc.	S-1	333-255754	May 4, 2021	
10.7†	License Agreement for RAF, effective as of December 16, 2019, by and between Sunesis Pharmaceuticals, Inc. and DOT Therapeutics-1, Inc.	S-1	333-255754	May 4, 2021	
10.8†	License Agreement, dated February 10, 2021, by and between Merck KGaA, Darmstadt, Germany and Day One Biopharmaceuticals, Inc.	S-1	333-255754	May 4, 2021	
10.9	Stock Exchange Agreement, dated May 4, 2021, by and between Day One Biopharmaceuticals Holding Co., LLC and Millennium Pharmaceuticals, Inc.	S-1	333-255754	May 4, 2021	
21.1	Subsidiaries of the Registrant				X
23.1	Consent of Independent Registered Public Accounting Firm.				X
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.				X
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.				X
32.1**	Certification of Principal Executive Officer and Principal Financial Officer Pursuant to 18 U.S.C. Section 1350, as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.				X
101.INS	Inline XBRL Instance Document				X
101.SCH	Inline XBRL Taxonomy Extension Schema Document				X
101.CAL	Inline XBRL Taxonomy Extension Calculation Linkbase Document.				X

101.DEF	Inline XBRL Taxonomy Extension Definition Linkbase Document.	X
101.LAB	Inline XBRL Taxonomy Extension Label Linkbase Document.	X
101.PRE	Inline XBRL Taxonomy Extension Presentation Linkbase Document.	X
104	Cover Page Interactive Data File (Embedded within the Inline XBRL document and included in Exhibit 101)	X

† Registrant has omitted portions of the exhibit as permitted under Item 601(b)(10) of Regulations S-K.

^ Indicates management contract or compensatory plan.

** This certification is deemed not filed for purposes of section 18 of the Exchange Act or otherwise subject to the liability of that section, nor shall it be deemed incorporated by reference into any filing under the Securities Act or the Exchange Act.

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 Report to be signed on its behalf by the undersigned, thereunto duly authorized**.**

DAY ONE BIOPHARMACEUTICALS, INC.

Date: March 6, 2023

By: /s/ Jeremy Bender, Ph.D., M.B.A.
Jeremy Bender, Ph.D., M.B.A.
Chief Executive Officer and President
(Principal Executive Officer)

DAY ONE BIOPHARMACEUTICALS, INC.

Date: March 6, 2023

By: /s/ Charles N. York II, M.B.A.
Charles N. York II, M.B.A.
Chief Operating Officer and Chief Financial Officer
(Principal Financial and Accounting Officer)

POWER OF ATTORNEY

KNOW ALL PERSONS BY THESE PRESENTS, that each person whose signature appears below hereby constitutes and appoints Jeremy Bender, Ph. D., M.B.A and Charles N. York II, M.B.A., and each of them, with full power of substitution and resubstitution and full power to act without the other, as his or her true and lawful attorney-in-fact and agent to act in his or her name, place and stead and to execute in the name and on behalf of each person, individually and in each capacity stated below, and to file 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, ratifying and confirming all that said attorneys-in-fact and agents or any of them or their or his substitute or 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 Report has been signed below by the following persons on behalf of the Registrant in the capacities and on the dates indicated.

Name	Title	Date
/s/ Jeremy Bender, Ph.D., M.B.A. Jeremy Bender, Ph.D., M.B.A.	Chief Executive Officer and President (Principal Executive Officer)	March 6, 2023
/s/ Charles N. York II, M.B.A. Charles N. York II, M.B.A.	Chief Operating Officer and Chief Financial Officer (Principal Financial and Accounting Officer)	March 6, 2023
/s/ Garry Nicholson, M.B.A. Garry Nicholson	Chair and Director	March 6, 2023
/s/ Julie Grant, M.Phil., M.B.A. Julie Grant, M.Phil., M.B.A.	Director	March 6, 2023
/s/ Dan Becker, M.D., Ph.D. Dan Becker, M.D., Ph.D.	Director	March 6, 2023
/s/ Scott Garland Scott Garland	Director	March 6, 2023
/s/ Michael Gladstone Michael Gladstone	Director	March 6, 2023
/s/ Natalie Holles Natalie Holles	Director	March 6, 2023
/s/ John A. Josey, Ph.D., M.B.A. John A. Josey, Ph.D., M.B.A.	Director	March 6, 2023
/s/ Saira Ramasastry, M.S., M.Phil. Saira Ramasastry, M.S., M.Phil.	Director	March 6, 2023

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Report of Independent Registered Public Accounting Firm

To the Members and the Board of Directors of
Day One Biopharmaceuticals, Inc.

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of Day One Biopharmaceuticals, Inc. (the Company) as of December 31, 2022 and 2021, the related consolidated statements of operations, comprehensive loss, redeemable convertible preferred shares, redeemable noncontrolling interest and stockholders' equity/members' (deficit) and cash flows for each of the three years in the period ended December 31, 2022, and the related notes (collectively referred to as the "consolidated financial statements"). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company at December 31, 2022 and 2021 and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2022, in conformity with U.S. generally accepted accounting principles.

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/ Ernst & Young LLP

We have served as the Company's auditor since 2021.

San Mateo, California
March 6, 2023

Day One Biopharmaceuticals, Inc.
Consolidated Balance Sheets
(in thousands, except share amounts)

	December 31, 2022	December 31, 2021
Assets		
Current assets:		
Cash and cash equivalents	$ 85,262	$ 284,309
Short-term investments	257,007	—
Prepaid expenses and other current assets	5,605	5,059
Total current assets	347,874	289,368
Property and equipment, net	20	57
Operating lease right-of-use asset	699	227
Deposits and other long-term assets	469	169
Total assets	$ 349,062	$ 289,821
Liabilities and stockholders' equity		
Current liabilities:		
Accounts payable	$ 260	$ 1,744
Accrued expenses and other current liabilities	15,950	6,709
Current portion of operating lease liabilities	405	204
Total current liabilities	16,615	8,657
Long-term portion of lease liabilities	408	16
Total liabilities	17,023	8,673
Commitments and contingencies (Note 6)		
Stockholders' equity:		
Common stock, $0.0001 par value; 500,000,000 shares authorized as of December 31, 2022 and 2021; 73,458,176 and 61,952,292 shares issued and outstanding as of December 31, 2022 and 2021, respectively	7	6
Additional paid-in-capital	601,771	408,629
Accumulated other comprehensive loss	(71)	—
Accumulated deficit	(269,668)	(127,487)
Total stockholders' equity	332,039	281,148
Total liabilities and stockholders' equity	$ 349,062	$ 289,821

The accompanying notes are an integral part of these consolidated financial statements.

Day One Biopharmaceuticals, Inc.
Consolidated Statements of Operations
(in thousands, except share and per share amounts)

	Year Ended December 31,		
	2022	2021	2020
Operating expenses:			
Research and development	$ 85,618	$ 43,584	$ 9,100
General and administrative	61,291	29,159	4,682
Total operating expenses	146,909	72,743	13,782
Loss from operations	(146,909)	(72,743)	(13,782)
Interest income (expense), net	4,746	4	(30)
Other expense, net	(18)	(15)	(31)
Changes in fair value of derivative tranche liability	—	—	(30,000)
Net loss	(142,181)	(72,754)	(43,843)
Net loss attributable to redeemable convertible noncontrolling interest	—	(2,109)	(3,336)
Exchange of redeemable noncontrolling interest shares – deemed dividend	—	(99,994)	—
Net loss attributable to common stockholders/members	$ (142,181)	$ (170,639)	$ (40,507)
Net loss per share, basic and diluted	$ (2.17)	$ (4.62)	$ (7.33)
Weighted-average number of common shares used in computing net loss per share, basic and diluted	65,466,773	36,960,569	5,529,519

The accompanying notes are an integral part of these consolidated financial statements.

Day One Biopharmaceuticals, Inc.
Consolidated Statements of Comprehensive Loss
(in thousands)

	Year Ended December 31,		
	2022	2021	2020
Net loss	$ (142,181)	$ (72,754)	$ (43,843)
Other comprehensive loss:			
Unrealized loss on available-for-sale securities	(71)	—	—
Total comprehensive loss	$ (142,252)	$ (72,754)	$ (43,843)

The accompanying notes are an integral part of these consolidated financial statements.

Day One Biopharmaceuticals, Inc.
Consolidated Statements of Redeemable Convertible Preferred Shares, Redeemable Noncontrolling Interest and Stockholders' Equity/ Members' (Deficit)
(in thousands, except share amounts)

	Redeemable Convertible Preferred Shares		Redeemable Noncontrolling	Common Stock		Common Shares		Incentive Shares		Additional Paid-In	Accumulated Other Comprehensive	Accumulated	Stockholders' Equity/Members'
	Shares	Amount	Interest	Shares	Amount	Shares	Amount	Shares	Amount	Capital	Loss	Deficit	(Deficit)
Balance at December 31, 2019	12,502,752	$ 30,504	$ 5,487	—	$ —	6,035,869	$ 2,000	1,488,421	$ 111	$ —	$ —	$ (12,784)	$ (10,673)
Issuance of Series A redeemable convertible preferred shares for cash, net of issuance costs of $22	10,348,505	29,977	—	—	—	—	—	—	—	—	—	—	—
Issuance of incentive shares	—	—	—	—	—	—	—	3,101,178	—	—	—	—	—
Cancellations of incentive shares	—	—	—	—	—	—	—	(477,582)	—	—	—	—	—
Reclassification of derivative tranches liability upon settlement	—	31,483	—	—	—	—	—	—	—	—	—	—	—
Share-based compensation expense	—	—	—	—	—	—	—	—	526	—	—	—	526
Net loss attributable to redeemable noncontrolling interest	—	—	(3,336)	—	—	—	—	—	—	—	—	—	—
Transfer to redeemable noncontrolling interest related to change in ownership	—	—	3,551	—	—	—	—	—	—	—	—	(3,551)	(3,551)
Net loss attributable to Day One Biopharmaceuticals Holding Company, LLC members	—	—	—	—	—	—	—	—	—	—	—	(40,507)	(40,507)
Balance at December 31, 2020	22,851,257	$ 91,964	$ 5,702	—	$ —	6,035,869	$ 2,000	4,112,017	$ 637	$ —	$ —	$ (56,842)	$ (54,205)
Issuance of Series B redeemable convertible preferred shares for cash, net of issuance costs of $243	9,638,141	129,757	—	—	—	—	—	—	—	—	—	—	—
Issuance of incentive shares	—	—	—	—	—	—	—	2,959,795	—	—	—	—	—
Cancellations of incentive shares	—	—	—	—	—	—	—	(265,596)	—	—	—	—	—
Conversion of redeemable convertible preferred, common, and incentive shares into common stock	(32,489,398)	(221,721)	—	43,958,557	4	(6,035,869)	(2,000)	(6,806,216)	(1,175)	224,892	—	—	221,721
Conversion of redeemable noncontrolling interest to common stock	—	—	(3,593)	6,470,382	1	—	—	—	—	3,592	—	—	3,593
Common stock issued in IPO, net of issuance costs of $16,995	—	—	—	11,500,000	1	—	—	—	—	167,044	—	—	167,045
Issuance of shares pursuant to Employee Stock Purchase Plan	—	—	—	23,353	—	—	—	—	—	318	—	—	318
Share-based compensation expenses	—	—	—	—	—	—	—	—	538	12,783	—	—	13,321
Net loss attributable to redeemable noncontrolling interest	—	—	(2,109)	—	—	—	—	—	—	—	—	—	—
Net loss attributable to common stockholders/members	—	—	—	—	—	—	—	—	—	—	—	(70,645)	(70,645)
Balance at December 31, 2021	—	$ —	$ —	61,952,292	$ 6	—	$ —	—	$ —	$ 408,629	$ —	$ (127,487)	$ 281,148
Issuance of common stock pursuant to follow-on offering, net of issuance costs of $10,864	—	—	—	11,500,000	1	—	—	—	—	161,609	—	—	161,610
Issuance of common stock upon exercise of stock options	—	—	—	235,474	—	—	—	—	—	3,649	—	—	3,649
Issuance of common stock upon release of restricted stock units	—	—	—	79,441	—	—	—	—	—	—	—	—	—
Issuance of common stock pursuant to Employee Stock Purchase Plan	—	—	—	97,413	—	—	—	—	—	642	—	—	642
Unvested common stock forfeiture	—	—	—	(406,444)	—	—	—	—	—	—	—	—	—
Share-based compensation expenses	—	—	—	—	—	—	—	—	—	27,242	—	—	27,242
Unrealized loss on available-for-sale securities	—	—	—	—	—	—	—	—	—	—	(71)	—	(71)
Net loss attributable to common stockholders/members'	—	—	—	—	—	—	—	—	—	—	—	(142,181)	(142,181)
Balance at December 31, 2022	—	$ —	$ —	73,458,176	$ 7	—	$ —	—	$ —	$ 601,771	$ (71)	$ (269,668)	$ 332,039

The accompanying notes are an integral part of these consolidated financial statements.

Day One Biopharmaceuticals, Inc.
Consolidated Statements of Cash Flows
(in thousands)

	Year Ended December 31,		
	2022	2021	2020
Cash flows from operating activities			
Net loss	$ (142,181)	$ (72,754)	$ (43,843)
Adjustments to reconcile net loss to net cash used in operating activities:			
Acquired in-process research and development assets	—	8,000	—
Share-based compensation expense	27,242	13,321	526
Depreciation expense	63	20	16
Accretion of discounts on short-term investments, net	(2,030)	—	—
Amortization of operating right-of-use assets	468	179	139
Non-cash interest expense	—	—	30
Changes in derivative tranche liabilities	—	—	30,000
Changes in operating assets and liabilities:			
Prepaid expenses and other current assets	(546)	(3,717)	(1,336)
Deposits and other long-term assets	(300)	(62)	(107)
Accounts payable	(1,484)	1,542	132
Accrued expenses and other current liabilities	9,241	5,114	1,127
Operating lease liabilities	(347)	(182)	(173)
Net cash used in operating activities	(109,874)	(48,539)	(13,489)
Cash flows from investing activities			
Cash paid for purchase of short-term investments	(394,206)	—	—
Proceeds from maturity of short-term investment	139,158	—	—
Cash paid for purchase of property and equipment	(26)	—	(92)
Cash paid for acquired in-process research and development assets	—	(8,000)	—
Net cash used in investing activities	(255,074)	(8,000)	(92)
Cash flows from financing activities			
Proceeds from issuance of Series A redeemable convertible preferred shares, net of issuance costs	—	—	29,977
Proceeds from issuance of Series B redeemable convertible preferred shares, net of issuance costs	—	129,757	—
Proceeds from issuance of common stock, net	161,610	167,045	—
Proceeds from issuance of common stock upon stock option exercises	3,649	—	—
Proceeds from issuance of common stock upon ESPP purchase	642	318	—
Net cash provided by financing activities	165,901	297,120	29,977
Net (decrease) increase in cash and cash equivalents	(199,047)	240,581	16,396
Cash and cash equivalents, beginning of period	284,309	43,728	27,332
Cash and cash equivalents, end of period	$ 85,262	$ 284,309	$ 43,728
Supplemental disclosures of noncash activities			
Lease liability obtained in exchange for right-of-use asset	940	$ —	$ 545
Transfers to redeemable convertible noncontrolling interest	$ —	$ —	$ 3,551
Exchange of 45,331,483 preferred, common, and incentive shares in connection with the Conversion (Note 1)	$ —	$ 224,892	$ —
Exchange of redeemable convertible noncontrolling interest to 6,470,382 shares of common stock (Note 11)	$ —	$ 3,592	$ —

The accompanying notes are an integral part of these consolidated financial statements.

1. Description of Business and Organization

Organization and Business

Day One Biopharmaceuticals, Inc., or the Company, is a clinical-stage biopharmaceutical company dedicated to developing and commercializing targeted therapies for patients of all ages with life-threatening diseases. The Company was formed as a limited liability company under the laws of the State of Delaware in November 2018, under the name Hero Therapeutics Holding Company, LLC. Subsequently, the Company changed its name to Day One Therapeutics Holding Company, LLC in December 2018 and to Day One Biopharmaceuticals Holding Company, LLC, or Day One Holding LLC, in March 2020.

On May 26, 2021, the Company completed a conversion by filing a certificate of conversion with the Secretary of State of the State of Delaware and changed its name to Day One Biopharmaceuticals, Inc. Prior to December 31, 2021, the Company had two subsidiaries: DOT Therapeutics-2, Inc. (formerly Hero Therapeutics Inc. and Day One Biopharmaceuticals, Inc.), or DOT-2, incorporated in Delaware in November 2018, and DOT Therapeutics-1, Inc., or DOT-1, incorporated in Delaware in December 2019. DOT-2 and DOT-1 are collectively referred to herein as the Subsidiaries.

In December 2021, the Company's board of directors approved the merger, or the Merger, of the Subsidiaries with and into the Company, with the Company being the surviving corporation, effective December 31, 2021. For more information on the financial statement impact of the Merger, refer to the section titled "Basis of Presentation."

Initial Public Offering, Corporate Conversion and Exchange of Takeda's shares

On June 1, 2021, the Company closed its initial public offering, or the IPO, in which it sold an aggregate of 11,500,000 shares of common stock at a price to the public of $16.00 per share, which included 1,500,000 shares issued upon the full exercise by the underwriters of their option to purchase additional shares of common stock. The Company received aggregate net proceeds from the IPO of $167.0 million, after deducting underwriting discounts and commissions and offering costs, of $17.0 million. The common stock began trading on the Nasdaq Global Select Market on May 27, 2021 under the symbol "DAWN."

In contemplation of the IPO, on May 26, 2021, the Company completed a legal entity conversion, or the Conversion, which included the following: Day One Holding LLC (i) converted from a Delaware limited liability company to a Delaware corporation by filing a certificate of conversion with the Secretary of State of the State of Delaware and (ii) changed its name to Day One Biopharmaceuticals, Inc.

As part of the Conversion:

- holders of Series A redeemable convertible preferred shares of Day One Holding LLC received one share of Series A redeemable convertible preferred stock of the Company for each Series A redeemable convertible preferred share held immediately prior to the Conversion;
- holders of Series B redeemable convertible preferred shares of Day One Holding LLC received one share of Series B redeemable convertible preferred stock of the Company for each Series B redeemable convertible preferred share held immediately prior to the Conversion;
- holders of common shares of Day One Holding LLC received one share of common stock of the Company for each common share held immediately prior to the Conversion;

- each outstanding incentive share in Day One Holding LLC converted into a number of shares of common stock of the Company based upon a conversion price determined by the board of directors. The conversion price was determined as a difference between the IPO price of $16.00 per share and the participating threshold for each incentive share. The Company issued 5,433,290 common stock shares upon the conversion of incentive shares of Day One Holding LLC, of which 4,719,605 common stock shares continue to vest as per the original vesting terms of the incentive shares awards.

In connection with the IPO and the Conversion, pursuant to the terms of the Millennium Stock Exchange Agreement, or the Millennium Stock Exchange Agreement, and the Conversion, Millennium Pharmaceuticals, Inc. exchanged 9,857,143 shares of Series A redeemable convertible preferred stock of DOT-1, a subsidiary of Day One Holding LLC, for 6,470,382 shares of common stock of the Company, or the Exchange.

The Company holds all property and assets of Day One Holding LLC and assumed all of the debts and obligations of Day One Holding LLC. Effective on the date of the Conversion, each member of the board of directors and each officer of Day One Holding LLC became a member of the board of directors and an officer of the Company. The Conversion was a tax-free reorganization, that included authorization to issue capital stock consisting of 500,000,000 shares of common stock, $0.0001 par value per share, and 10,000,000 shares of undesignated preferred stock, $0.0001 par value per share.

Upon the closing of the IPO, 32,489,398 shares of redeemable convertible preferred stock issued by the Company in the Conversion converted into an equal number of shares of common stock. The Company also granted options for 4,418,874 shares of common stock at an exercise price of $16.00 per share upon the IPO date.

Shares Split

On May 23, 2021, the board of directors of Day One Holding LLC approved an amendment to its operating agreement to effect a forward split of the Company’s shares at a 2.325-for-1 ratio, or the Stock Split. The Stock Split became effective on May 23, 2021, upon approval by the members and execution of the amended LLC operating agreement. All issued and outstanding common shares, redeemable convertible preferred shares, incentive shares and per share amounts contained in these consolidated financial statements have been retroactively adjusted to reflect this Stock Split for all periods presented.

Risks and Uncertainties Related to COVID-19

The full impact of the ongoing COVID-19 pandemic remains highly uncertain and subject to change. There are many uncertainties around the COVID-19 pandemic and future developments, which are unpredictable, may result in a material, negative impact to the Company's operations and financial condition. The Company has experienced and expect to continue to experience volatility in services rendered from its third-party service providers as local governments respond to resurgences and the emergence of new strains, each of which may result in the prolonged reinstitution, extension or enhancement of protective measures. With respect to manufacturing and supply, the Company does not anticipate disruptions to its drug supply chain, and it cannot be sure if lock-down measures or restrictions will be implemented and what, if any, impact that may have on its facilities and operations.

The Company's management team continues to actively monitor this evolving health crisis and its effects on its operations, key vendors and workforce.

2. Summary of Significant Accounting Policies

Basis of Presentation

The accompanying consolidated financial statements are prepared in conformity with accounting principles generally accepted in the United States of America, or U.S. GAAP, and include the accounts of the Company’s subsidiaries. All intercompany transactions and balances have been eliminated in consolidation.

Because the Merger (refer to the section "Organization and Business") did not constitute a change in the reporting entity, as defined in Accounting Standard Codification, or ASC, 250, *Accounting changes and error corrections*, the Company has reported the assets and liabilities transferred from its Subsidiaries at historical carrying value, prospectively from December 31, 2021.

Any reference in these notes to applicable guidance is meant to refer to the authoritative GAAP as found in ASC and Accounting Standards Updates, or ASU, of the Financial Accounting Standards Board, or FASB.

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 reported amounts of assets, liabilities and disclosure of contingent assets and liabilities at the date of the consolidated financial statements, and the reported amounts of expenses during the reporting period. Significant estimates and assumptions made in the accompanying consolidated financial statements include, but are not limited to, the valuation of share-based awards, the valuation of deferred tax assets and income tax uncertainties, and accruals for research and development activities. The Company bases its estimates on historical experience and on various other assumptions that are believed to be reasonable. Actual results may differ from those estimates or assumptions.

Segments

The Company has determined that its chief executive officer is the chief operating decision maker, or CODM. The Company operates and manages the business as one reporting and one operating segment, which is the business of identifying and advancing targeted therapies for patients of all ages with genomically defined cancers. The Company's CODM reviews financial information on an aggregate basis for purposes of allocating resources and evaluating financial performance. All of the Company's assets are located in the United States.

Concentration of credit risk and other risks and uncertainties

Financial instruments that subject the Company to significant concentrations of credit risk consist primarily of cash, cash equivalents and short-term investments. The Company's cash, cash equivalents and short-term investments are held in more than one financial institution in the United States. Amounts on deposit may at times exceed federally insured limits. Management believes that the financial institutions that the Company's cash, cash equivalents and short-term investments are held at are financially sound and, accordingly, minimal credit risk exists with respect to the financial institutions.

The Company is subject to certain risks and uncertainties and believes that changes in any of the following areas could have a material adverse effect on the Company's future financial position or results of its operations: ability to obtain future financing; regulatory requirements for approval and market acceptance of, and reimbursement for, product candidates; performance of third-party clinical research organizations and manufacturers upon which the Company relies; development of sales channels; protection of the Company's intellectual property; litigation or claims against the Company based on intellectual property, patent, product, regulatory or other factors; changes to the market landscape; and the Company's ability to attract and retain employees necessary to support its growth.

The Company is dependent on third-party manufacturers to supply products for research and development activities in its programs. In particular, the Company relies and expects to continue to rely on a small number of manufacturers to supply it with its requirements for the active pharmaceutical ingredients and formulated drugs related to these programs. These programs could be adversely affected by a significant interruption in the supply of active pharmaceutical ingredients and formulated drugs.

Cash and Cash Equivalents

The Company considers all highly liquid investments with an original maturity of three months or less at the time of purchase to be cash equivalents. The Company's cash equivalents consist of investments in money market funds and U.S. government agency securities. Cash equivalents are recognized at amortized cost, which approximates fair value.

Investments

The Company's investments are comprised of U.S. government agency securities and U.S. treasury securities. Investments are classified at the time of purchase, based on management's intent, as held-to-maturity, available-for-sale, or trading. All of the Company's investments are classified as available-for-sale. Available-for-sale securities are carried at estimated fair value with unrealized holdings gains and losses (net of tax effects) on such investments reported in other comprehensive (loss) income as a separate component on the consolidated statements of comprehensive loss. Fair value is determined based on quoted market rates when observable or by utilizing data points that are observable, such as quoted prices, interest rates, and yield curves.

For available-for-sale securities, the Company determines if any impairment is related to credit loss or non-credit loss. In making the assessment of whether a loss is from credit or other factors, management considers the extent to which fair value is less than amortized cost, any changes to the rating of the security by a rating agency and adverse conditions related to the security, among other factors. If this assessment indicates that a credit loss exists, the present value of cash flows expected to be collected from the security are compared to the amortized cost basis of the security. If the present value of cash flows is less than the amortized cost basis, a credit loss exists and an allowance is created, limited by the amount that the fair value is less than amortized cost basis. Subsequent activity related to the credit loss component in the form of write-offs or recoveries is recognized as part of the allowance for credit losses on available-for-sale securities.

Fair Value of Financial Instruments

Assets and liabilities recorded at fair value on a recurring basis in the consolidated balance sheets are categorized based upon the level of judgment associated with the inputs used to measure their fair values. Fair value is defined as the exchange price that would be received for an asset or an exit price that would be paid to transfer a liability in the principal or most advantageous market for the asset or liability in an orderly transaction between market participants on the measurement date. Valuation techniques used to measure fair value must maximize the use of observable inputs and minimize the use of unobservable inputs. The authoritative guidance on fair value measurements establishes a three-tier fair value hierarchy for disclosure of fair value measurements as follows:

Level 1—Observable inputs such as unadjusted, quoted prices in active markets for identical assets or liabilities at the measurement date;

Level 2—Inputs (other than quoted prices included in Level 1) are either directly or indirectly observable for the asset or liability. These include quoted prices for similar assets or liabilities in active markets and quoted prices for identical or similar assets or liabilities in markets that are not active; and

Level 3—Unobservable inputs that are supported by little or no market activity and that are significant to the fair value of the assets or liabilities.

To the extent that the valuation is based on models or inputs that are less observable or unobservable in the market, the determination of fair value requires more judgment. Accordingly, the degree of judgment exercised by the Company in determining fair value is greatest for instruments categorized in Level 3. A financial instrument's level within the fair value hierarchy is based on the lowest level of any input that is significant to the fair value measurement.

The carrying amounts reflected in the accompanying consolidated balance sheets for cash equivalents, prepaid expenses, other current assets, accounts payable, accrued expenses and other current liabilities approximate their fair values, due to their short-term nature.

Property and Equipment, Net

Property and equipment are recorded at cost, less accumulated depreciation and amortization. Depreciation is recognized using the straight-line method over the estimated useful lives of the related assets ranging from three to five years, and leasehold improvements are amortized over the shorter of the lease term or the estimated useful life of the asset.

Leases

Contractual arrangements that meet the definition of a lease are classified as operating or finance leases and are recorded on the consolidated balance sheets as both a right-of-use asset, or ROU asset, and lease liability, calculated by discounting fixed lease payments over the lease term at the rate implicit in the lease or the Company's incremental borrowing rate, or IBR. Lease ROU assets and lease obligations are recognized based on the present value of the future minimum lease payments over the lease term at commencement date. The Company currently does not have any finance leases.

Operating lease ROU assets are adjusted for (i) payments made at or before the commencement date, (ii) initial direct costs incurred, and (iii) tenant incentives under the lease. As the implicit rate for the operating leases are not determinable, the Company determines its IBR based on the information available at the applicable lease commencement date. The IBR is determined by using the rate of interest that the Company would pay to borrow on a collateralized basis an amount equal to the lease payments for a similar term and in a similar economic environment where the asset is located. The Company considers a lease term to be the noncancelable period that it has the right to use the underlying asset, including any periods where it is reasonably certain the Company will exercise any option to extend the contract.

Lease costs for minimum lease payments for operating leases are recognized on a straight-line basis over the lease term. Lease liabilities are increased by interest and reduced by payments each period, and the ROU asset is amortized over the lease term. Variable lease costs are recorded when incurred. In measuring the ROU assets and lease liabilities, the Company has elected to combine lease and non-lease components. The Company excludes short-term leases, if any, having initial terms of 12 months or less at lease commencement as an accounting policy election, and recognizes rent expense on a straight-line basis over the lease term for these types of leases.

Impairment of Long-Lived Assets

The Company evaluates long-lived assets, which consist of property and equipment and right-of-use assets, for impairment whenever events or changes in circumstances indicate that the carrying amount of such assets may not be recoverable. Recoverability of assets to be held and used is measured by a comparison of the carrying amount of an asset to the future undiscounted net cash flows expected to be generated by the asset. If such assets are considered to be impaired, the impairment to be recognized is measured by the amount by which the carrying amount of the asset exceeds the fair value of the asset. To date, no impairments have been recognized in the consolidated financial statements.

Research and Development Expenses

Research and development expenses consist of costs associated with acquiring technology and intellectual property licenses that have no alternative future uses; costs incurred under agreements with third-party contract research organizations, contract manufacturing organizations and other third parties that conduct clinical trials on the Company's behalf; other costs associated with research and development programs, including laboratory materials and supplies; employee-related costs, including salaries, benefits and share-based compensation expense, for the Company's research and development personnel; and facilities and other overhead expenses, including expenses for rent and facilities maintenance, and amortization. The Company's expense research and development costs as incurred. The Company is obligated to make upfront payments upon execution of certain research and development agreements. Advance payments, including nonrefundable amounts, for goods or services that will be used or rendered for future research and development activities are deferred. Such amounts are recognized as expense as the related goods are delivered or the related services are performed, or such time when the Company does not expect the goods to be delivered or services to be performed.

Accrued Research and Development Expenses

The Company records accrued liabilities for estimated costs of research and development activities conducted by third-party service providers, which include the conduct of preclinical and clinical studies, and contract manufacturing activities. The Company records the estimated costs of research and development activities based upon the estimated amount of services provided but not yet invoiced and includes these costs in accrued liabilities in the balance sheets and within research and development expenses in the consolidated statements of operations. These costs are a significant component of our research and development expenses. The Company accrues for these costs based on factors such as estimates of the work completed and in accordance with agreements established with third-party service providers under the service agreements. The Company makes judgments and estimates in determining the accrued liabilities balance in each reporting period. As actual costs become known, the Company adjusts its accrued liabilities. The Company has not experienced any material differences between accrued costs and actual costs incurred.

The Company makes payments in connection with clinical trials under contracts with contract manufacturing organizations and contract research organizations that support conducting and managing clinical trials. The financial terms of these contracts are subject to negotiation, which vary by contract and may result in payments that do not match the periods over which materials or services are provided. Generally, these agreements set forth the scope of work to be performed at a fixed fee, unit price or on a time and materials basis. In the event the Company makes advance payments for goods or services that will be used or rendered for future research and development activities, the payments are deferred and capitalized as a prepaid expense and recognized as expense as the goods are received or the related services are rendered. Such payments are evaluated for current or long-term classification based on when they are expected to be realized.

Patent Costs

All patent-related costs incurred in connection with filing and prosecuting patent applications are expensed as incurred due to the uncertainty of the recovery of the expenditure. Amounts incurred are classified as general and administrative expenses in the consolidated statements of operations.

Redeemable Convertible Preferred Shares

The Company recorded redeemable convertible preferred shares at their respective fair values on the dates of issuance, net of issuance costs. The redeemable convertible preferred shares were recorded outside of members' deficit because while they were not mandatorily redeemable, in the event of a deemed liquidation event, which was outside of the Company's control, the proceeds were distributed first to the redeemable convertible preferred shareholders in accordance with their liquidation preferences. The Company had not adjusted the carrying values of the redeemable convertible preferred shares to their liquidation preferences because it is uncertain whether or when a deemed liquidation event would occur that would obligate it to pay the liquidation preferences to holders of redeemable convertible preferred shares. Redeemable convertible preferred shares were all converted to common stock shares upon the closing of the IPO in May 2021.

Redeemable Noncontrolling Interest

Redeemable noncontrolling interest represented the portion of equity (net assets) in DOT-1 that was neither directly nor indirectly attributable to the Company. Redeemable noncontrolling interest is classified as temporary equity because preferred shares issued to a holder contained certain redemption features that were not solely within the control of the Company.

Share-Based Compensation

Prior to the IPO, the Company recognized share-based compensation expense based on the estimated fair value of all share-based awards, incentive shares and restricted share awards, on the date of grant using the option-pricing model. The option-pricing model requires the input of subjective assumptions, including the fair value of the underlying common shares, the expected term of the award, the expected volatility, risk-free interest rates, and the dividend yield. In determining the fair value of common shares, the methodologies used to estimate the enterprise value were performed using methodologies, approaches, and assumptions consistent with the American Institute of Certified Public Accountants Accounting and Valuation Guide, *Valuation of Privately-Held-Company Equity Securities Issued as Compensation*. The participation threshold amounts were determined by the board of directors, at the time of grant. The expected life of the awards granted during the period was determined based on an expected time to the liquidation event. The Company applied the risk-free interest rate based on the U.S. Treasury yield in effect at the time of the grant consistent with the life of the award. The expected volatility was based on a peer group in the industry in which the Company did business consistent with the expected time to liquidity. The dividend yield was set at zero as the underlying security did not and was not expected to pay a dividend.

Subsequent to closing of the IPO, the Company uses the Black-Scholes valuation model to estimate the fair value of options granted to employees and non-employees, intrinsic value to estimate the fair value of restricted stock award, and fair value of the Company's common stock at the grant date for restricted stock units.

The Black-Scholes option-pricing model, used to estimate fair value of stock options awards, requires the use of the following assumptions:

- *Fair Value of Common Stock*—The Company's closing price on the Nasdaq market at the grant date.
- *Expected Term*—The expected term represents the period that the share-based awards are expected to be outstanding. The expected term for stock options is calculated using the simplified method, as the weighted-average vesting term of the award and the award's contract period. The Company utilizes this method due to lack of historical exercise data and the plain-vanilla nature of the Company's service condition share-based awards. For the Company's performance condition stock option awards, the Company calculated the expected term by taking into consideration the options' contractual life, the timing of when milestones are expected to be achieved, and the expected exercise period by a holder from the vesting date until the contractual term.
- *Expected Volatility*—Since the Company does not have sufficient trading history for its common stock, the expected volatility is estimated based on the average historical volatilities of common stock of comparable publicly traded biopharmaceutical companies over a period equal to the expected term of the stock option grants. The comparable biopharmaceutical companies are chosen based on their size, stage in the life cycle or area of specialty. The Company will continue to apply this process until sufficient historical information regarding the volatility of the common stock price becomes available.
- *Risk-Free Interest Rate*—The risk-free interest rate is based on the U.S. Treasury yield in effect at the time of grant for zero-coupon U.S. Treasury notes with maturities approximately equal to the expected term of the awards.
- *Expected Dividend Yield*—The Company has never paid dividends on the common stock and has no plans to pay dividends on its common stock. Therefore, the expected dividend yield use is zero.

The Company uses the straight-line attribution method for recognizing share-based compensation expense. The Company recognizes forfeitures by reducing the expense in the same period the forfeitures occur. The Company recognizes share-based compensation expense for awards with performance conditions when it is probable that the condition will be met, and the award will vest. The Company classifies share-based compensation expense in the consolidated statements of operations in the same manner in which the award recipients' payroll costs are classified or in which the award recipients' service payments are classified.

Income Taxes

Prior to the IPO, the Company was a "pass-through" entity under the Internal Revenue Code with two corporate subsidiaries. Prior to the Conversion, the members of the Company, formerly Day One Biopharmaceuticals Holding Company, LLC, were taxed directly on their respective ownership interests and activity in Day One Biopharmaceuticals Holding Company, LLC. The Company's consolidated corporate subsidiaries accounted for income taxes under the asset and liability method, as discussed below.

Upon the closing of the IPO and the Conversion, the Company's income taxes are accounted for under the asset and liability method. Deferred tax assets and liabilities are recognized for the future tax consequences attributable to differences between the financial statement carrying amounts of existing assets and liabilities and their respective tax base and net operating loss and tax credit carryforwards. Deferred tax assets and liabilities are determined based upon the difference between the consolidated financial statement carrying amounts and the tax basis of assets and liabilities and are measured using the enacted tax rate expected to apply to taxable income in the years in which the differences are expected to be reversed. Deferred tax assets are reduced by a valuation allowance if it is more likely than not that some portion or all of the deferred tax asset will not be realized.

The uncertain income tax positions are recognized at the largest amount that is more likely than not to be sustained upon audit by the relevant taxing authority. Changes in recognition or measurement are reflected in the period in which judgment occurs. The Company's policy is to recognize interest and penalties related to the underpayment of income taxes as a component of the provision for income taxes. To date, there have been no interest or penalties recorded in relation to unrecognized tax benefits.

Net Loss per Share

The Company calculates basic and diluted net loss per share in conformity with the two-class method required for participating securities. Under the two-class method, basic net loss per share is computed by dividing the net loss by the weighted average number of common shares outstanding during the period, without consideration of potential dilutive securities. Diluted net loss per share is computed by dividing the net loss, after adjusting it for loss attributable to redeemable noncontrolling interest, in any, by the sum of the weighted average number of common stock shares outstanding during the period plus the dilutive effects of potentially dilutive securities outstanding during the period. Potentially dilutive securities include incentive shares, unvested restricted common shares and redeemable convertible preferred shares, prior to the IPO. Potentially dilutive securities include unvested restricted stock awards, unvested restricted stock units and stock options, after the IPO. For all periods presented, diluted net loss per share is the same as basic net loss per share since the effect of including potential common stock shares is anti-dilutive and incentive shares participation thresholds were not met.

Comprehensive Loss

Comprehensive loss represents all changes in stockholders' equity except those resulting from and distributions to stockholders. The Company's unrealized gains and losses on available-for-sale securities represent the only component of other comprehensive loss that are excluded from the reported net loss and that are presented in the consolidated statements of comprehensive loss.

Emerging Growth Company Status

The Company is an emerging growth company, as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act. Under the JOBS Act, emerging growth companies can delay adopting new or revised accounting standards issued subsequent to the enactment of the JOBS Act until such time as those standards apply to private companies. The Company has elected to use this extended transition period for complying with new or revised accounting standards that have different effective dates for public and private companies until the earlier of the date that it (i) is no longer an emerging growth company or (ii) affirmatively and irrevocably opts out of the extended transition period provided in the JOBS Act. As a result, these consolidated financial statements may not be comparable to companies that comply with the new or revised accounting pronouncements as of public company effective dates.

The JOBS Act does not preclude an emerging growth company from adopting a new or revised accounting standard earlier than the time that such standard applies to private companies. The Company expects to use the extended transition period for any other new or revised accounting standards during the period in which it remains an emerging growth company.

Recently Adopted Accounting Pronouncements

In December 2019, the FASB issued ASU 2019-12, Income Taxes (Topic 740): Simplifying the Accounting for Income Taxes, or ASU 2019-12, which eliminates certain exceptions related to the approach for intra-period tax allocation, the methodology for calculating income taxes in an interim period and the recognition of deferred tax liabilities for outside basis differences. ASU 2019-12 also clarifies and simplifies other aspects of the accounting for income taxes. The standard is effective for fiscal years, and interim periods within those fiscal years, beginning after December 15, 2020, with early adoption permitted. The Company adopted ASU 2019-12 on January 1, 2022, and this adoption had no material impact on the Company's financial statements and related disclosures.

3. Recurring Fair Value Measurements

The following table sets forth the Company's financial instruments as of December 31, 2022 and 2021, which are measured at fair value on a recurring basis by level within the fair value hierarchy (in thousands):

	December 31, 2022			
	Level 1	Level 2	Level 3	Total
Financial assets:				
Money market funds	$ 18,765	$ —	$ —	$ 18,765
U.S. treasury securities	—	145,785	—	145,785
U.S. government agency securities	—	136,022	—	136,022
Total assets measured at fair value	$ 18,765	$ 281,807	$ —	$ 300,572

	December 31, 2021			
	Level 1	Level 2	Level 3	Total
Financial assets:				
Money market funds	$ 111,221	$ —	$ —	$ 111,221
Total assets measured at fair value	$ 111,221	$ —	$ —	$ 111,221

The Company's money market funds are classified as Level 1 because they are measured using observable inputs from active markets for identical assets.

The Company's U.S. treasury securities and U.S. government agency securities are classified as Level 2 because they are measured with inputs that are either directly or indirectly observable for the asset which include quoted prices for similar assets in active markets and quoted prices for identical or similar assets in markets that are not active.

There were no assets or liabilities classified as Level 3 as of December 31, 2022 and 2021.

There were no transfers between Level 1, Level 2 or Level 3 categories during the periods presented.

The following tables summarize the estimated fair value of the Company's cash equivalents, available-for-sale securities classified as short-term investments, and associated unrealized gains and losses (in thousands):

	December 31, 2022			
	Amortized Cost	Unrealized Gains	Unrealized Losses	Estimated Fair Value
Cash equivalents:				
Money market funds	$ 18,765	$ —	$ —	$ 18,765
U.S. government agency securities	24,800	—	—	24,800
Total cash equivalents	43,565	—	—	43,565
Short-term investments				
U.S. treasury securities	145,880	1	(96)	145,785
U.S. government agency securities	111,197	37	(12)	111,222
Total short-term investments	$ 257,077	$ 38	$ (108)	$ 257,007

	December 31, 2021			
	Amortized Cost	Unrealized Gains	Unrealized Losses	Estimated Fair Value
Cash equivalents:				
Money market funds	$ 111,221	$ —	$ —	$ 111,221
Total cash equivalents	$ 111,221	$ —	$ —	$ 111,221

The following table summarizes the maturities of our cash equivalents and available-for-sale securities as of December 31, 2022 (in thousands):

	Amortized Cost	Fair Value
Mature in one year or less	$ 300,642	$ 300,572
Total	$ 300,642	$ 300,572

The following table presents the breakdown of the Company's available-for-sale securities with gross unrealized losses and the duration that those losses had been unrealized as December 31, 2022 (in thousands):

	December 31, 2022					
	Unrealized Losses Less Than 12 Months		Unrealized Losses 12 Months or Greater		Total	
	Fair Value	Unrealized Losses	Fair Value	Unrealized Losses	Fair Value	Unrealized Losses
Financial assets:						
U.S. treasury securities	$ 140,822	$ (96)	$ —	$ —	$ 140,822	$ (96)
U.S. government agency securities	26,811	(12)	—	—	26,811	(12)
Total financial assets	$ 167,633	$ (108)	$ —	$ —	$ 167,633	$ (108)

The Company did not have available-for-sale securities with gross unrealized losses as of December 31, 2021.

The Company regularly reviews the changes to the rating of its securities and monitors the surrounding economic conditions to assess the risk of expected credit losses. As of December 31, 2022, there were no securities that were in an unrealized loss position for more than 12 months. As of December 31, 2022, the unrealized losses on the Company’s investments in U.S. treasury securities and U.S. government securities were caused by interest rate increases. The current credit ratings are all within the guidelines of the investment policy of the Company and the Company does not expect the issuers to settle any security at a price less than the amortized cost basis of the investment with the contractual cash flows of these investments guaranteed by the issuer. No allowance for credit losses has been recorded since it is not more likely than not that the Company will be required to sell the investments before recovery of their amortized cost basis.

4. Balance Sheet Items

Prepaid Expenses and Other Current Assets

Prepaid and other current assets consisted of the following (in thousands):

	December 31, 2022	December 31, 2021
Prepaid research and development expenses	$ 3,007	$ 2,099
Prepaid insurance	1,592	1,945
Other prepaid expenses and other assets	1,006	1,015
Total prepaid expenses and other current assets	$ 5,605	$ 5,059

Property and Equipment, Net

Property and equipment, net, consisted of the following (in thousands):

	December 31, 2022	December 31, 2021
Leasehold improvements	$ 26	$ 15
Furniture and fixtures	—	78
Property and equipment, gross	26	93
Less: accumulated depreciation	(6)	(36)
Property and equipment, net	$ 20	$ 57

Depreciation expense for the years ended December 31, 2022, 2021, and 2020 was approximately $63,000, $20,000, and $16,000, respectively.

Accrued Expenses and Other Current Liabilities

Accrued expenses and other current liabilities consisted of the following (in thousands):

	December 31, 2022	December 31, 2021
Accrued research and development expenses	$ 7,554	$ 3,308
Accrued payroll related expenses	6,129	2,565
Accrued professional service expenses	2,088	732
Other	179	104
Total accrued expenses and other current liabilities	$ 15,950	$ 6,709

5. Significant Agreements

License agreement with Merck KGaA, Darmstadt, Germany

On February 10, 2021, DOT-2, the Company's subsidiary, entered into a license agreement, or the MRKDG License Agreement, with Merck KGaA, Darmstadt, Germany, a pharmaceutical corporation located in Darmstadt, Germany. Under the MRKDG License Agreement, Merck KGaA, Darmstadt, Germany granted to the Company an exclusive worldwide license, with the right to grant sublicenses through multiple tiers, under specified patent rights and know-how for the Company to research, develop, manufacture and commercialize products containing and comprising the pimasertib and MSC2015103B compounds. The Company also received clinical inventory supplies to use in its research and development activities. The Company's exclusive license grant is subject to a non-exclusive license granted by Merck KGaA, Darmstadt, Germany's affiliate to a cancer research organization and Merck KGaA, Darmstadt, Germany retains the right to conduct, directly or indirectly, certain ongoing clinical studies relating to pimasertib.

Under the MRKDG License Agreement, the Company has obligations to use commercially reasonable efforts to develop and commercialize at least two licensed products in at least two specified major market countries by the year 2029.

In consideration for the rights granted under the MRKDG License Agreement and clinical supplies, the Company made an upfront payment of $8.0 million, which was recorded as research and development expenses, as the technology does not have an alternative future use and supplies are used for research activities. Additionally, the Company made a milestone payment of $2.5 million, which was recorded as research and development expenses due to the nature of the license agreement and the milestone event relating to the first dosing of a patient in a first clinical trial of a product containing pimasertib, in the year ended December 31, 2022. The Company may also be required to make additional payments of up to $364.5 million based upon the achievement of specified development, regulatory, and commercial milestones, as well a high, single-digit royalty percentage on future net sales of licensed products, if any. Milestones and royalties are contingent upon future events and will be recorded when the milestones are achieved and when payments are due.

The term of the MRKDG License Agreement will expire on a licensed product-by-licensed product and country-by-country basis upon the expiration of the Company's obligation to pay royalties to the licensor with respect to such licensed product in such country and will expire in its entirety upon the expiration of all of the Company's payment obligations with respect to all licensed products and all countries under the MRKDG License Agreement.

Effective December 31, 2021, DOT-2 was merged with and into the Company, with the Company being the surviving corporation and assuming DOT-2's obligations under the MRKDG License Agreement.

Takeda Asset Purchase Agreement

On December 16, 2019, DOT-1, the Company's subsidiary, entered into an asset purchase agreement, or the Takeda Asset Agreement, with Millennium Pharmaceuticals, Inc., a related party and an affiliate of Takeda Pharmaceutical Company Limited, or Takeda. Pursuant to the Takeda Asset Agreement, DOT-1 purchased certain technology rights and know-how related to TAK-580 (which is now tovorafenib (DAY101)) that provides a new approach for treating patients with primary brain tumors or brain metastases of solid tumors. DOT-1 also received clinical inventory supplies to use in the Company's research and development activities of such RAF-inhibitor and an assigned investigator clinical trial agreement. Takeda also assigned to DOT-1 its exclusive license agreement, or the Viracta License Agreement, with Viracta Therapeutics, Inc. (f/k/a Sunesis Pharmaceuticals, Inc.), or Viracta. Takeda also granted DOT-1 a worldwide, sublicensable exclusive license under specified patents and know-how and non-exclusive license under other patents and know-how generated by Takeda under the Takeda Asset Agreement. The Company also granted Takeda a grant back license, as defined in the Takeda Asset Agreement, which is terminable either automatically or by DOT-1 in the event Takeda does not achieve specified development milestones within the applicable timeframes set forth under the Takeda Asset Agreement. This grant back license to Takeda was terminated at the time of Conversion in connection with the Millennium Stock Exchange Agreement.

In consideration for the sale and assignment of assets and the grant of the license under the Takeda Asset Agreement, DOT-1 made an upfront payment of $1.0 million in cash and issued 9,857,143 shares of Series A redeemable convertible preferred stock in DOT-1 in December 2019. The fair value of issued shares was estimated as $9.9 million, based on the price paid by other investors for issued shares in the Series A financing of DOT-1. Based on the terms of the Millennium Stock Exchange Agreement, Takeda exchanged the 9,857,143 shares of Series A redeemable convertible preferred stock of DOT-1 for 6,470,382 shares of the Company's common stock upon the effectiveness of the Conversion, on May 26, 2021.

The term of the Takeda Asset Agreement will expire on a country-by-country basis upon expiration of all assigned patent rights and all licensed patent rights in such country. Takeda may terminate the Takeda Asset Agreement prior to the Company's first commercial sale of a product if we cease conducting any development activities for a continuous and specified period of time and such cessation is not agreed upon by the parties and is not done in response to guidance from a regulatory authority. Additionally, Takeda can terminate the Takeda Asset Agreement in the event of the Company's bankruptcy. In the event of termination of the Takeda Asset Agreement by Takeda as a result of our cessation of development or bankruptcy, all assigned patents, know-how and contracts (other than the Viracta License Agreement) will be assigned back to Takeda and Takeda will obtain a reversion license under patents and know-how generated to exploit all such terminated products.

Effective December 31, 2021, DOT-1 was merged with and into the Company, with the Company being the surviving corporation and assuming DOT-1's obligations under the Takeda Assets Purchase Agreement.

Viracta License Agreement

On December 16, 2019, DOT-1 amended and restated the Viracta License Agreement that was assigned pursuant to the Takeda Asset Agreement. Under the Viracta License Agreement, DOT-1 received a worldwide exclusive license under specified patent rights and know-how to develop, use, manufacture, and commercialize products containing compounds binding the RAF protein family.

DOT-1 paid $2.0 million upfront in cash to Viracta, which was recorded as research and development expenses in 2019. DOT-1 made a milestone payment of $3.0 million to Viracta in February 2021, which was recorded as research and development expense when the milestone was achieved in April 2021. DOT-1 is also required to make additional milestone payments of up to $54.0 million upon achievement of specified development and regulatory milestones for each licensed product in two indications, with milestones payable for the second indication to achieve a specified milestone event being lower than milestones payable for the first indication. Additionally, if DOT-1 obtains a priority review voucher with respect to a licensed product and sells such priority review voucher to a third party or uses such priority review voucher, DOT-1 is obligated to pay Viracta a specified percentage in the mid-teen digits of all net consideration received from any such sale or of the value of such used priority review voucher, as applicable. Commencing on the first commercial sale of a licensed product in a country, DOT-1 is obligated to pay tiered royalties ranging in the mid-single-digit percentages on net sales of licensed products, if any. The obligation to pay royalties will end on a country-by-country and licensed product-by-licensed product basis commencing on the first commercial sale in a country and continuing until the later of: (i) the expiration of the last valid claim of the Viracta licensed patents, jointly owned collaboration patents or specified patents owned by the Company covering the use or sale of such product in such country, (ii) the expiration of the last statutory exclusivity pertaining to such product in such country or (iii) the tenth anniversary of the first commercial sale of such product in such country. No other milestones, except as discussed above, were achieved and due as of December 31, 2022.

The term of the Viracta License Agreement will expire on a licensed product-by-licensed product and country-by-country basis upon the expiration of the Company’s obligation to pay royalties to Viracta with respect to such product in such country. DOT-1 has the right to terminate the Viracta License Agreement with respect to any or all of the licensed products at will upon a specified notice period.

Effective December 31, 2021, DOT-1 was merged with and into the Company, with the Company being the surviving corporation and assuming DOT-1’s obligations under Viracta License Agreement.

6. Commitments and Contingencies

Leases

The Company entered into a lease agreement for its corporate office facility in South San Francisco, California in March 2020. Such agreement was determined to be a lease, since the right to control the use of the identified asset was conveyed to the Company for a period of time in exchange for consideration. The Company can extend the lease term for an additional three years at market rates upon the notice of extension. The Company is obligated to pay monthly rent expense and its pro rata share of utilities, common area maintenance expenses, and property taxes. The landlord also provided an allowance of $10,000 for tenant improvements. The Company concluded that it is an operating lease. Common area expenses are a non-lease component and a variable consideration and included in operating expenses as incurred. The extension period has not been included in the determination of the Right of Use, or ROU, asset or the lease liability for operating leases as the Company concluded that it is not reasonably certain that it would exercise this option. In October 2022, the Company terminated this lease agreement prior to its scheduled expiration in January 2023.

In April 2022, the Company entered into a lease agreement for approximately 12,000 square feet of general use office space in Brisbane, California. Such agreement was determined to be a lease since the right to control the use of the identified asset was conveyed to the Company for a period of time in exchange for consideration. The term of the lease is 31 months and commenced in May 2022. There is no option to extend the lease term nor is there an option to terminate the lease term prior to its expiration. The Company is obligated to pay monthly rent expense and its pro rata share of the landlord's operating expenses which include utilities, common area maintenance expenses, and property taxes. Such expenses are a non-lease component and a variable consideration and included in the Company's operating expenses as incurred. The Company concluded that this lease is also an operating lease. The total payments for base rent over the term of the lease is approximately $1.1 million. Upon execution of the

agreement, the Company paid a security deposit of approximately $40,000 classified as deposits and other long-term assets on the consolidated balance sheet.

The Company determined the lease incremental borrowing rate, or IBR, based on the information available at the applicable lease commencement date as the Company's leases do not provide an implicit rate. The IBR is determined by using the rate of interest that the Company would pay to borrow on a collateralized basis an amount equal to the lease payments for a similar term and in a similar economic environment where the asset is located. As of December 31, 2022, the weighted-average remaining lease term and weighted-average discount rate were 1.9 years and 9.0%, respectively.

The Company's lease does not require any contingent rental payments, impose financial restrictions, or contain any residual value guarantees.

Lease expense of right-of-use assets is recognized on a straight-line basis over the applicable lease term. Lease expense was $0.5 million, $0.2 million and $0.1 million for the years ended December 31, 2022, 2021 and 2020, respectively. Cash paid for amounts included in the measurement of operating lease liabilities was $0.4 million, $0.2 million and $0.2 million for the years ended December 31, 2022, 2021 and 2020, respectively. Variable payments expensed during the years ended December 31, 2022, 2021, and 2020 were immaterial.

As of December 31, 2022, the future lease obligations were as follows (in thousands):

2023	$	458
2024		424
Total future minimum lease payments		882
Less: Imputed interest		69
Present value of operating lease liabilities	$	813

Research and Development Agreements

The Company enters into contracts in the normal course of business with clinical research organizations, contract manufacturing organizations, and other third-party vendors for clinical trial, manufacturing, testing, and other research and development activities. These contracts generally provide for termination on notice, with the exception of one vendor where certain costs are non-cancellable after the approval of the project. As of each of December 31, 2022 and 2021, there were no amounts accrued related to termination and cancellation charges as these are not probable.

License Agreements

The Company entered into the license agreements, as disclosed in Note 5, pursuant to which the Company is required to pay milestones contingent upon meeting of specific events. The first milestone, related to the Viracta License Agreement, was achieved and recorded to research and development expense during the year ended December 31, 2021. The second milestone, related to the MRKDG License Agreement, was achieved and recorded to research and development during the year ended December 31, 2022. The Company may be required to pay royalties on sales of products developed under these agreements. All products are in development as of December 31, 2022 and 2021, and no such royalties were due.

Legal Proceedings

The Company, from time to time, may be party to litigation arising in the ordinary course of business. The Company is not subject to any material legal proceedings, and to the best of its knowledge, no material legal proceedings are currently pending or threatened.

Indemnification Agreements

In the normal course of business, the Company enters into contracts and agreements that contain a variety of representations and warranties and provide for indemnification for certain liabilities. The exposure under these agreements is unknown because it involves claims that may be made against it in the future but have not yet been made. To date, the Company has not paid any claims or been required to defend any action related to its indemnification obligations. However, the Company may record charges in the future as a result of these indemnification obligations. The Company also has indemnification obligations to its directors and executive officers for specified events or occurrences, subject to some limits, while they are serving at its request in such

capacities. There have been no claims, to date and the Company believes the fair value of these indemnification agreements is minimal. Accordingly, the Company had not recorded any liabilities for these agreements as of each of December 31, 2022 and 2021.

7. Redeemable Convertible Preferred Shares

On June 1, 2021, the Company completed its IPO, selling an aggregate of 11,500,000 shares of common stock. All outstanding redeemable convertible preferred shares were converted into 32,489,398 shares of common stock upon the completion of the IPO. As of December 31, 2022, the Company did not have any outstanding shares of redeemable convertible preferred shares.

In February 2021, the Company issued 9,638,141 Series B redeemable convertible preferred shares at a price of $13.488 per share for gross cash proceeds of $130.0 million. The Company incurred issuance costs of $243,000.

8. Common Stock

Pursuant to its certificate of incorporation, the Company is authorized to issue 500.0 million shares of common stock at a par value of $0.0001 per share. As of December 31, 2022, 73,458,176 shares of common stock were issued and outstanding.

In November 2018, the Company entered into common shares purchase agreements with two founders of the Company. The individuals purchased a total of 2,790,000 common shares for a total purchase price of $300. Shares vested monthly for two and four years, respectively. Vesting for a certain number of shares was accelerated upon the Company's closing of its Series A redeemable convertible preferred share financing. The Company also has an option for a period of ninety days after the individual's employment is terminated either voluntarily or involuntarily to repurchase the unvested common shares at a price that is the lower of the original price per share paid by the founder for such stock or the fair value as of the date of such repurchase. The founders' shares were converted to common stock in the Conversion. As of December 31, 2022, all founders' common stock were vested.

At-The-Market Offering

In June 2022, the Company entered into an equity distribution agreement with Piper Sandler & Co. and JonesTrading Institutional Services LLC, as sales agents, relating to the issuance and sale of shares of the Company's common stock for an aggregate offering price of up to $150.0 million under an at-the-market offering program, or the 2022 ATM. During the year ended December 31, 2022, the Company did not make any sales under the 2022 ATM.

June 2022 Follow-On Offering

In June 2022, the Company completed a follow-on offering and issued and sold 11,500,000 shares of common stock (including the exercise by the underwriters of their option to purchase an additional 1,500,000 shares of common stock) at a price to the public of $15.00 per share for net proceeds of approximately $161.6 million, after deducting underwriting discounts, commissions, and offering costs.

The Company has reserved shares of common stock for future issuances as follows:

	December 31, 2022
Common stock options issued and outstanding	7,634,167
Common stock available for future grants	1,839,775
Common stock available for ESPP	1,101,756
Restricted stock units issued and outstanding	485,351
Total	11,061,049

9. Share-Based Compensation

Prior to the Conversion, Day One Holding LLC granted incentive shares under the Incentive Share Plan and was authorized to issue 8,924,177 incentive shares. Incentive shares were a separate non-voting class of shares that participated in distributions only after incentive shares vested, unless it was approved by the board of directors and included at least two of the preferred members, and a participation threshold was met. The incentive shares represented profits interests in Day One Holding LLC, which was an interest in the increase in the Company's value over the participation threshold, as defined in its operating agreement and as determined at the time of grant. A holder of incentive shares had the right to participate in distributions of profits only in excess of the participation threshold. The participation threshold was based on the valuation of the Company's common shares on or around the grant date.

The fair value of the incentive shares was estimated using an option pricing model with the following assumptions:

	Year Ended December 31,	
	2021	2020
Common share fair value	$6.36 - $8.89	$0.85 - $2.10
Participating threshold	$6.36 - $7.51	$0.27
Risk free rate	0.14%	0.16% - 0.30%
Volatility	72.90%	78.00% - 80.00%
Time to liquidity (in years)	0.20 - 1.80	3.03 - 3.33
Grant date fair value	$4.24 - $4.52	$0.71 - $1.67

During the Conversion, the Company converted all incentive shares to vested and unvested shares of common stock. As such, there was no incentive shares activity for the year ended December 31, 2022.

The Company used the option pricing model to estimate the fair value of each incentive shares award on the date of grant. The members' equity value was based on a recent enterprise valuation analysis performed and common share fair value. The participation threshold amounts were determined by the board of directors at the time of grant. The expected life of the awards granted during the period was determined based on an expected time to the liquidation event. The Company applied the risk-free interest rate based on the U.S. Treasury yield in effect at the time of the grant.

Fair Value of Common Share

Prior to the IPO, management's approach to estimate the fair value of the common share was consistent with the methods outlined in the American Institute of Certified Public Accountants' Practice Aid, *Valuation of Privately-Held-Company Equity Securities Issued as Compensation*, or the Practice Aid, considering a number of objective and subjective factors including: valuations of common shares performed with the assistance of independent third-party valuation specialists; the Company's stage of development and business strategy, including the status of research and development efforts, and the material risks related to the business and industry; the Company's results of operations and financial position, including levels of available capital resources; the valuation of publicly traded companies in the life sciences and biotechnology sectors, as well as recently completed mergers and acquisitions of peer companies; the lack of marketability of the common shares; the prices of redeemable convertible preferred shares sold to investors in arm's length transactions and the rights, preferences, and privileges of the Company's redeemable convertible preferred shares relative to those of common shares; the likelihood of achieving a liquidity event for the holders of the common and redeemable convertible preferred shares, such as an initial public offering or a sale, given prevailing market conditions. The fair value of the common shares was approved by the board of directors until such time as the Company shares were listed on an established stock exchange or national market system.

The incentive shares were classified as equity awards and share-based compensation expense was based on the grant date fair value of the award.

The following table provides a summary of the incentive shares activity:

	Number of Shares	Weighted Average Grant Date Fair Value
Outstanding as of December 31, 2020	4,112,017	$ 1.26
Granted	2,959,795	$ 4.32
Forfeited	(265,596)	$ 1.67
Converted to unvested common stock	(6,806,216)	$ 2.58
Outstanding as of December 31, 2021	—	$ —

2022 Equity Inducement Plan

In October 2022, the board of directors and stockholders approved the 2022 Equity Inducement Plan, or the 2022 Plan. The 2022 Plan provides for the grant of non-statutory stock options and restricted stock units. The number of shares of common stock reserved for issuance under the 2022 Plan is 1,000,000 shares.

The following table provides a summary of stock option activity under the 2022 Plan during the year ended December 31, 2022.

	Options	Weighted-Average Exercise Price Per Share	Weighted-Average Remaining Contractual Term	Aggregate Intrinsic Value (in thousands)
Outstanding at December 31, 2021	—	$ —		
Granted	309,000	$ 21.14		
Exercised	—	$ —		$ —
Forfeiture	—	$ —		
Outstanding at December 31, 2022	309,000	$ 21.14	9.8	$ 117
Vested and expected to vest at December 31, 2022	309,000	$ 21.14	9.8	$ 117
Exercisable at December 31, 2022	—	$ —	—	$ —

Aggregate intrinsic value represents the difference between the estimated fair value of the underlying common stock and the exercise price of outstanding, in-the-money options.

There was no fair value of options that vested during the years ended December 31, 2022, 2021 and 2020. The weighted-average grant date fair value of options granted during the year ended December 31, 2022 was $15.08 per share. There was no weighted-average grant date fair value of options granted during the years ended December 31, 2021 and 2020.

Unamortized share-based compensation for stock options as of December 31, 2022 was $4.5 million, which is expected to be recognized over a weighted-average period of 3.8 years.

The Company used the Black-Scholes option pricing model to estimate the fair value of stock options awards granted with the following assumptions:

	Year Ended December 31, 2022
Expected term (in years)	6.08
Expected volatility	79.53%
Risk-free interest rate	4.18%
Expected dividend yield	—

The following table provides a summary of restricted stock units activity under the 2022 Plan during the year ended December 31, 2022:

	Number of Shares	Weighted Average Grant Date Fair Value Per Share
Unvested restricted stock units at December 31, 2021	—	$ —
Granted	47,400	$ 21.14
Vested	—	$ —
Forfeiture	—	$ —
Unvested restricted stock units at December 31, 2022	47,400	$ 21.14

Unamortized share-based compensation for restricted stock units as of December 31, 2022 was $1.0 million, which is expected to be recognized over a weighted-average period of 3.9 years.

2021 Equity Incentive Plan

Immediately prior to consummation of the IPO, all the outstanding incentive shares were converted into common stock. The following table provides a summary of the unvested common stock awards activity during the year ended December 31, 2022.

	Number of Shares	Weighted Average Grant Date Fair Value Per Share
Unvested common stock as of December 31, 2021	3,753,862	$ 16.00
Vested	(1,624,674)	$ 16.00
Forfeiture	(406,444)	$ 16.00
Unvested common stock as of December 31, 2022	1,722,744	$ 16.00

In May 2021, in connection with the IPO, the board of directors and stockholders approved, the 2021 Equity Incentive Plan, or the 2021 Plan, which became effective on the day before the date of the effectiveness of the IPO. The 2021 Plan provides for the grant of incentive stock options, non-statutory stock options, stock appreciation rights, awards of restricted stock, restricted stock units and other share-based awards. The number of shares of common stock reserved for issuance under the 2021 Plan is equal to the sum of: (x) 6,369,000 shares of common stock; plus (y) 4,719,605 shares of common stock issued in respect of the Conversion of incentive shares that were subject to vesting immediately prior to the effectiveness of the registration statement for the IPO that expire, terminate or are otherwise surrendered, canceled, forfeited or repurchased by us at their original issuance price pursuant to a contractual repurchase right. The number of shares available for grant and issuance under the 2021 Plan will be automatically increased on the first day of each fiscal year, beginning with the fiscal year commencing on January 1, 2021 and continuing for each fiscal year until, and including, the fiscal year commencing on January 1, 2031, by the lesser of (a) 5% of the number of shares of all classes of the Company's common stock, plus the total number of shares of Company common stock issuable upon conversion of any preferred stock or exercise of any warrants to acquire shares of Company common stock for a nominal exercise price issued and outstanding on each December 31 immediately prior to the date of increase or (b) such number of shares determined by the board of directors.

The following table provides a summary of stock option activity under the 2021 Plan during the year ended December 31, 2022.

	Options	Weighted-Average Exercise Price Per Share	Weighted-Average Remaining Contractual Term	Aggregate Intrinsic Value (in thousands)
Outstanding at December 31, 2021	5,071,896	$ 16.90		
Granted	3,284,580	$ 15.45		
Exercised	(235,474)	$ 15.70		$ 1,604
Forfeiture	(486,835)	$ 15.17		
Outstanding at December 31, 2022	7,634,167	$ 16.42	8.8	$ 40,759
Vested and expected to vest at December 31, 2022	7,634,167	$ 16.42	8.8	$ 40,759
Exercisable at December 31, 2022	2,287,512	$ 16.46	8.6	$ 12,050

Aggregate intrinsic value represents the difference between the estimated fair value of the underlying common stock and the exercise price of outstanding, in-the-money options.

The total fair value of options that vested during the years ended December 31, 2022 and 2021 was $23.1 million and $1.1 million, respectively. There was no fair value of options that vested during the year ended December 31, 2020. The weighted-average grant date fair value of options granted during the years ended December 31, 2022 and 2021 were $9.61 per share and $9.91 per share, respectively. There was no weighted-average grant date fair value of options granted during the year ended December 31, 2020.

Unamortized share-based compensation for stock options as of December 31, 2022 was $49.8 million, which is expected to be recognized over a weighted-average period of 2.7 years.

The Company used the Black-Scholes option pricing model to estimate the fair value of stock options awards granted with the following assumptions:

	Year Ended December 31,	
	2022	2021
Expected term (in years)	5.27 - 6.33	5.31 - 6.08
Expected volatility	65.20% - 81.68%	61.25% - 66.53%
Risk-free interest rate	1.47% - 4.37%	0.82% - 1.39%
Expected dividend yield	—	—

The following table provides a summary of restricted stock units activity under the 2021 Plan during the year ended December 31, 2022:

	Number of Shares	Weighted Average Grant Date Fair Value Per Share
Unvested restricted stock units at December 31, 2021	96,890	$ 22.93
Granted	503,095	$ 15.47
Vested	(79,441)	$ 16.82
Forfeiture	(35,193)	$ 14.14
Unvested restricted stock units at December 31, 2022	485,351	$ 16.83

Unamortized share-based compensation for restricted stock units as of December 31, 2022 was $7.5 million, which is expected to be recognized over a weighted-average period of 3.3 years.

Performance Awards

In June 2022, the Company granted performance awards, consisting of performance stock options, or PSOs, and performance stock units, or PSUs, to non-executive employees pursuant to the 2021 Equity Incentive Plan. Each performance award is earned through the achievement of a performance-based metric over a defined performance period determined by the compensation committee of the Company's board of directors. The estimated fair value of the equity awards that contain performance conditions is expensed over the term of the award once the Company has determined that it is probable that the performance conditions will be satisfied. During the year ended December 31, 2022, the Company granted 152,550 PSOs with a weighted-average grant date fair value of $7.78 per share and 99,250 PSUs with a weighted-average grant date fair value of $15.25 per share. The total fair values of PSOs and PSUs granted were $1.2 million and $1.5 million, respectively. As of December 31, 2022, no PSOs or PSUs had vested since the achievement of the performance-based metrics of the performance awards was not deemed probable.

The Company used the Black-Scholes option pricing model to estimate the fair value of the PSO awards granted with the following assumptions:

	Year Ended December 31, 2022
Expected term (in years)	2.92 - 3.42
Expected volatility	72.72% - 72.98%
Risk-free interest rate	3.37%
Expected dividend yield	—

2021 Employee Stock Purchase Plan

In May 2021, the board of directors adopted and the stockholders approved the 2021 Employee Stock Purchase Plan, or the ESPP, which became effective on May 26, 2021. A total of 603,000 shares of common stock were initially reserved for issuance under the ESPP. The number of shares of the common stock reserved for issuance under the ESPP will automatically increase on the first day of each fiscal year, beginning with the fiscal year commencing on January 1, 2021 and continuing for each fiscal year until, and including, the fiscal year commencing on January 1, 2031, by the lesser of: (a) 1% of the total number of outstanding shares of common stock of the Company (on an as converted basis outstanding on the immediately preceding December 31 (rounded down to the nearest whole share) and (b) an amount determined by the board of directors. 97,413 shares have been issued under the ESPP as of December 31, 2022. The Company recognized $0.5 million and $0.2 million of compensation expense related to the ESPP plan for the years ended December 31, 2022 and 2021, respectively. The Company did not recognize any compensation expense related to the ESPP plan for the year ended December 31, 2020.

The fair value of our common stock to be issued under the ESPP is estimated at the date of grant using a Black-Scholes option-pricing model with the following assumptions:

	Year Ended December 31,	
	2022	2021
Expected term (in years)	0.50	0.25 - 0.50
Expected volatility	128.95%	42.5% - 48.4%
Risk-free interest rate	4.54%	0.05% - 0.06%
Expected dividend yield	—	—

Share-based compensation expense recorded in the accompanying consolidated statements of operations is as follows (in thousands):

	Year Ended December 31,		
	2022	2021	2020
Research and development expense	$ 8,486	$ 3,840	$ 212
General and administrative expense	18,756	9,481	314
Total share-based compensation expense	$ 27,242	$ 13,321	$ 526

As of December 31, 2022, there was $70.1 million of unrecognized compensation cost related to unvested restricted stock, unvested restricted stock units, unvested stock options, and shares subject to purchase under the ESPP that is expected to be recognized over a weighted-average period of approximately 2.8 years.

As of December 31, 2022, there was $2.6 million of unrecognized compensation cost related to unvested PSOs and PSUs. The Company will recognize the PSO and PSU expense through the expected vesting dates when the achievement of the performance-based metrics is probable.

10. Net Loss Per Share

Basic and diluted net loss per share attributable to common shareholders/stockholders after the Conversion is calculated as follows (in thousands except share and per share amounts):

	Twelve Months Ended December 31,		
	2022	2021	2020
Net loss	$ (142,181)	$ (72,754)	$ (43,843)
Net loss attributable to redeemable convertible noncontrolling interests	—	(2,109)	(3,336)
Exchange of redeemable noncontrolling interest shares – deemed dividend	—	(99,994)	—
Net loss attributable to common stockholders/members	(142,181)	(170,639)	(40,507)
Net loss per share, basic and diluted	$ (2.17)	$ (4.62)	$ (7.33)
Weighted-average number of common shares used in computing net loss per share, basic and diluted	65,466,773	36,960,569	5,529,519

The following outstanding potentially dilutive securities have been excluded from the calculation of diluted net loss per share, as their effect is anti-dilutive:

	As of December 31,		
	2022	2021	2020
Stock options	7,943,167	5,071,896	—
Unvested common shares	1,722,744	3,753,862	193,766
Restricted stock units	532,751	96,890	—
Shares committed under ESPP	44,672	25,362	—
Redeemable convertible preferred shares	—	—	22,851,257
Incentive shares	—	—	4,112,017
Total	10,243,334	8,948,010	27,157,040

11. Redeemable Noncontrolling Interest

Prior to the Merger, DOT-1, the Company's subsidiary, issued Series A redeemable convertible preferred shares to Takeda in accordance with the Takeda Asset Agreement (Note 5). The Company concluded that it represented a redeemable noncontrolling interest.

The Company adjusted the carrying value of redeemable noncontrolling interest to allocate net losses of the subsidiary to Takeda. Transfers to and from the redeemable noncontrolling interest represented changes in ownership and the allocation of Series A redeemable convertible preferred shares issuance costs issued by the subsidiary.

On May 26, 2021, pursuant to the terms of the Millennium Stock Exchange Agreement, Takeda exchanged 9,857,143 shares of Series A redeemable convertible preferred stock in DOT-1 for 6,470,382 shares of common stock of the Company. Prior to the Exchange, the Company accounted for the redeemable noncontrolling interest as discussed in the paragraph above and allocated $2.1 million of net losses to Takeda for the period from January 1, 2021 to May 26, 2021. The Exchange resulted in DOT-1 becoming a wholly owned subsidiary of the Company and was recorded for accounting purposes as an extinguishment of the redeemable noncontrolling interest. As such, the Company also recognized an extinguishment loss of $100.0 million to additional paid-in-capital, which was calculated as a difference between the fair value of common stock issued to Takeda in the conversion and the carrying value of redeemable noncontrolling interest at the conversion date. The all-stock exchange was treated as a deemed dividend in the calculation of net loss attributable to common stockholders/members and net loss per share.

12. Income Taxes

Prior to the IPO and conversion, the Company was treated as a partnership for tax purposes, and thus, not subject to income taxes. It was the responsibility of the LLC members to report their proportion share of any taxable income or loss generated by Day One Biopharmaceuticals Holdings Company, LLC to the appropriate taxing authorities and pay the associated taxes, if any. Prior to the Conversion, the Company's consolidated subsidiaries were treated as corporations for tax purposes and were subject to income taxes which have been included in the consolidated financial statements. Subsequent to the Conversion, the Company and its subsidiaries are treated as a consolidated corporate group for tax purposes. On December 31, 2021, the Company liquidated the prior subsidiaries into the Company in a tax-free Internal Revenue Code Section 332 liquidation. As such, a single entity provision and subsequent tax return is calculated for the year ended December 31, 2022. All pre-tax losses have been incurred in the United States.

The effective tax rate of the Company's provision (benefit) for income taxes differs from the federal statutory rate as follows:

	Year Ended December 31,		
	2022	2021	2020
Statutory rate	21.0%	21.0%	21.0%
State tax	0.6%	(0.8)%	2.3%
Permanent differences	—	0.6%	(14.4)%
Credits	1.7%	3.8%	1.4%
Change in valuation allowance	(22.6)%	(21.5)%	(10.1)%
Share-based compensation	(0.7)%	(3.1)%	(0.2)%
Total	—	—	—

Deferred income taxes reflect the net effects of temporary differences between the carrying amounts of assets and liabilities for financial reporting purposes and the amounts used for income tax purposes. The principal components of the Company's deferred tax assets and liabilities consisted of the following (in thousands):

	As of December 31,		
	2022	2021	2020
Deferred tax assets			
Federal and state net operating loss carryforwards	$ 25,884	$ 17,270	$ 7,732
Capitalized R&D Section 174 Expense	14,908	—	—
Credits	6,653	3,670	731
Intangible asset basis	2,562	2,188	—
Share-based compensation	2,133	—	—
Accrued expenses	1,803	709	235
Total deferred tax assets	53,943	23,837	8,698
Total deferred tax liabilities	(149)	(59)	(97)
Less: valuation allowance	(53,794)	(23,778)	(8,601)
Net deferred tax assets	$ —	$ —	$ —

The Company has incurred net operating losses in each year since inception. The Company has not reflected the benefit of any such net operating loss carryforwards in the consolidated financial statements. Due to its history of losses, and lack of other positive evidence, the Company determined that it is more likely than not that its net deferred tax assets will not be realized, and therefore, the net deferred tax assets are fully offset by a valuation allowance at December 31, 2022 and 2021. The Company increased the valuation allowance by $30.0 million, $15.2 million and $4.4 million for the years ended December 31, 2022, 2021, and 2020, respectively.

As of December 31, 2022, the Company had federal net operating loss carryforwards, or NOLs, of $117.6 million that do not expire and federal tax credits of $8.2 million available to offset tax liabilities that begin to expire in 2038. The Company also has gross state NOLs of $17.6 million and state tax credits of $1.2 million which are available to offset state tax liabilities. The state NOLs begin to expire in 2038 and the state tax credits do not expire.

The Company has not completed a study to determine whether an ownership change per the provisions of Section 382 of the Internal Revenue Code, as well as similar state provisions, has occurred. Utilization of its net operating loss and income tax credit carryforwards may be subject to a substantial annual limitation due to

ownership changes that may have occurred or that could occur in the future. These ownership changes may limit the amount of the net operating loss and income tax credit carryover that can be utilized annually to offset future taxable income. In general, an "ownership change" as defined by Section 382 of the Internal Revenue Code results from a transaction or series of transactions over a three-year period resulting in an ownership change of more than 50 percentage points of the outstanding shares of a company by certain shareholders.

In accordance with the Tax Cuts and Jobs Act of 2017, Research and Experimental, or R&E, expenses under Internal Revenue Code Section 174 are required to be capitalized beginning in 2022. R&E expenses are required to be amortized over a period of 5 years for domestic expenses and 15 years for foreign expenses.

Uncertain Tax Positions

In accordance with authoritative guidance, the impact of an uncertain income tax position on the income tax return must be recognized at the largest amount that is more-likely-than-not to be sustained upon audit by the relevant taxing authority. An uncertain income tax position will not be recognized if it has less than a 50% likelihood of being sustained.

The following table reconciles the beginning and ending amount of unrecognized tax benefits (in thousands):

	Year Ended December 31,		
	2022	2021	2020
Balance at beginning of year	$ 1,141	$ 188	$ 2
Additions based on tax positions related to prior year	726	—	—
Additions based on tax positions related to current year	916	953	186
Reductions based on tax positions related to prior year	(248)	—	—
Reductions based on tax positions related to current year	—	—	—
Balance at end of year	$ 2,535	$ 1,141	$ 188

The entire amount of the unrecognized tax benefits would not impact the Company's effective tax rate if recognized. The Company has elected to include interest and penalties as a component of tax expense. During the years ended December 31, 2022, 2021 and 2020, the Company did not recognize accrued interest and penalties related to unrecognized tax benefits. The Company does not anticipate that the amount of existing unrecognized tax benefits will significantly increase or decrease during the next 12 months.

The Company files income tax returns in the U.S. federal, California and other state tax jurisdictions. The federal and state income tax returns from December 31, 2018 to December 31, 2022 remain subject to examination.

13. Defined Contribution Plan

The Company maintains an employee savings plan pursuant to Section 401(k) of the Internal Revenue Code. All employees are eligible to participate provided that they meet the requirements of the plan. For the year ended December 31, 2022, the Company made matching contributions of $0.8 million. The Company did not make matching contributions in the prior year.