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 001-38898

Applied Therapeutics, Inc.

(Exact name of registrant as specified in its charter)

Delaware	**81-3405262**
(State or Other Jurisdiction of Incorporation or Organization)	(I.R.S. Employer Identification No.)
545 Fifth Avenue, Suite 1400, New York, NY	**10017**
(Address of Principal Executive Offices)	(Zip Code)

Registrant's telephone number, including area code **(212)-220-9226**

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 $0.0001 par value	**APLT**	The Nasdaq Global 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 Section 15(d) of the Act. Yes ☐ No ☒

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

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

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

Large accelerated filer ☐ 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 approximate aggregate market value of voting stock held by non-affiliates of the registrant, based upon the last sale price of the registrant's common stock on the last business day of the registrant's most recently completed second fiscal quarter, June 30, 2022, as reported on The Nasdaq Global Market, was approximately $27,814,183. This calculation excludes approximately 18,677,687 shares held by directors, executive officers and 10% or greater shareholders of the registrant. Exclusion of these shares does not constitute a determination that each such person is an affiliate of the registrant.

As of March 22, 2023, the total number of shares outstanding of the registrant's Common Stock was 48,113,561 shares, net of treasury shares.

Documents Incorporated by Reference: Portions of the registrant's definitive proxy statement for the registrant's 2023 annual meeting, to be filed within 120 days after the close of the registrant's fiscal year, are incorporated by reference into Part III of this Annual Report on Form 10-K.

APPLIED THERAPEUTICS, INC.
2022 FORM 10-K ANNUAL REPORT

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CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K (this "Annual Report") may contain "forward-looking statements" within the meaning of the federal securities laws made pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995 about us and our industry that involve substantial risks and uncertainties. All statements other than statements of historical fact contained in this Annual Report, including statements regarding our strategy, future financial condition, future operations, projected costs, prospects, plans, objectives of management and expected market growth, are forward-looking statements. In some cases, you can identify forward-looking statements by terminology such as "aim," "anticipate," "assume," "believe," "contemplate," "continue," "could," "design," "due," "estimate," "expect," "forecast," "goal," "intend," "may," "objective," "opportunity," "plan," "predict," "project," "positioned," "potential," "seek," "should," "target," "will," "would" and other similar expressions that are predictions of or indicate future events and future trends, or the negative of these terms or other comparable terminology.

We have based these forward-looking statements largely on our current expectations and projections about future events and financial trends that we believe may affect our financial condition, results of operations, business strategy and financial needs. These forward-looking statements are subject to a number of known and unknown risks, uncertainties and assumptions, including risks described in the section titled "Risk Factors" in this Annual Report:

- our plans to develop, market and commercialize our product candidates;
- the initiation, timing, progress and results of our current and future preclinical studies and clinical trials and our research and development programs;
- our ability to take advantage of expedited regulatory pathways for any of our product candidates;
- our estimates regarding expenses, future revenue, capital requirements and needs for additional financing;
- our ability to successfully acquire or license additional product candidates on reasonable terms and advance product candidates into, and successfully complete, clinical studies;
- our ability to maintain and establish collaborations or obtain additional funding;
- our ability to obtain and timing of regulatory approval of our current and future product candidates;
- the anticipated indications for our product candidates, if approved;
- our expectations regarding the potential market size and the rate and degree of market acceptance of such product candidates;
- our ability to fund our working capital requirements and expectations regarding the sufficiency of our capital resources;
- the implementation of our business model and strategic plans for our business and product candidates;
- our intellectual property position and the duration of our patent rights;
- developments or disputes concerning our intellectual property or other proprietary rights;
- the potential impact of the Covid-19 pandemic on the timing and progress of our ongoing clinical trials, our business, results of operations, liquidity, and operations and our ability to mitigate those potential impacts;
- our expectations regarding government and third-party payor coverage and reimbursement;
- our ability to compete in the markets we serve;
- the impact of government laws and regulations and liabilities thereunder;
- developments relating to our competitors and our industry; and

- other factors that may impact our financial results.

The foregoing list of risks is not exhaustive. Other sections of this Annual Report include additional factors that could harm our business and financial performance. Moreover, we operate in a very competitive and rapidly changing environment. New risk factors emerge from time to time, and it is not possible for our management to predict all risk factors 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, or implied by, any forward-looking statements.

In light of the significant uncertainties in these forward-looking statements, you should not rely upon forward-looking statements as predictions of future events. Although we believe that we have a reasonable basis for each forward-looking statement contained in this Annual Report, 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 at all. You should refer to the sections titled "Risk Factors" and "Management's Discussion and Analysis of Financial Condition and Results of Operations" for a discussion of important factors that may cause our actual results to differ materially from those expressed or implied by our forward-looking statements. Furthermore, if our forward-looking statements prove to be inaccurate, the inaccuracy may be material. Except as required by law, we undertake no obligation to publicly update any forward-looking statements, whether as a result of new information, future events or otherwise.

Unless the context otherwise requires, the terms "Applied," "Applied Therapeutics," "the Company," "we," "us," "our", "the registrant" and similar references in this Annual Report on Form 10-K refer to Applied Therapeutics, Inc.

PART I

ITEM 1. BUSINESS.

Overview

We are a clinical-stage biopharmaceutical company developing a pipeline of novel product candidates against validated molecular targets in indications of high unmet medical need. We focus on molecules and pathways whose role in the disease process is well known based on prior research, but have previously failed to yield successful products due to poor efficacy and tolerability. Our unique approach to drug development leverages recent technological advances to design improved drugs, employs early use of biomarkers to confirm biological activity and focuses on abbreviated regulatory pathways. Our first molecular target is aldose reductase, or AR, an enzyme that converts glucose to sorbitol under oxidative stress conditions, and is implicated in multiple diseases. Prior attempts to inhibit this enzyme were hindered by nonselective, nonspecific inhibition, which resulted in limited efficacy and significant off-target safety effects. The detrimental consequences of AR activation have been well established by decades of prior research. Our AR program currently includes three small molecules, which are all potent and selective inhibitors of AR, but are engineered to have unique tissue permeability profiles to target different disease states, including diabetic complications, heart disease and rare metabolic diseases. The result of this unique multifaceted approach to drug development is a portfolio of highly specific and selective product candidates that we believe are significantly de-risked and can move quickly through the development process.

AT-007 is a novel central nervous system, or CNS, penetrant ARI that we are developing for the treatment of rare metabolic diseases, including Galactosemia and Sorbitol Dehydrogenase (SORD) Deficiency. Galactosemia is a devastating rare pediatric metabolic disease that affects how the body processes a simple sugar called galactose, and for which there is no known cure or approved treatment available. The U.S. Food and Drug Administration, or FDA, has granted both orphan drug designation and rare pediatric disease designation to AT-007 for the treatment of Galactosemia and in June 2021, the FDA granted Fast Track Designation to AT-007 for the treatment of Galactosemia. We have completed an adult study in healthy volunteers and Galactosemia patients, demonstrating that AT-007 is safe and well tolerated, and significantly reduces plasma galactitol levels vs. placebo. Galactitol is a toxic metabolite of galactose, which is formed in Galactosemia patients by aberrant activity of AR when galactose is present at high levels. A pediatric study is underway in children with Galactosemia, assessing the impact of AT-007 vs. placebo on safety, biomarker reduction of galactitol, and long-term functional outcomes. On April 13, 2021, we presented data featuring a cross-sectional analysis of nineteen pediatric patients with Classic Galactosemia, providing meaningful insight on the progressive worsening of the central nervous system phenotype with age. On October 18, 2021, we reported biomarker data from the pediatric ACTION-Galactosemia Kids study. The results demonstrate a substantial reduction in plasma galactitol of approximately 40%, which was statistically significant ($p<0.001$) vs. placebo. We previously reported a baseline analysis of the 47 children enrolled in the study which demonstrated a clear correlation between baseline galactitol levels and baseline clinical functional outcomes. The long-term functional outcomes portion of the pediatric study is ongoing, and the outcomes are assessed every 6 months by a fire-walled data monitoring committee (DMC). When the study reaches statistical significance in the active treated arm vs. the placebo arm, the DMC will alert the Company and the trial will be unblinded. Statistical modelling suggests that this should occur at approximately the 18-month outcome assessment, based on currently available predictive information. In April 2022, the Company met with the FDA to discuss the design of the ongoing pediatric study prior to the first 6-month outcomes assessment by the DMC. The FDA confirmed that the pediatric study as it is currently designed would support an NDA submission if statistical significance is reached, and there is alignment between the FDA and the Company on the potential path forward to approval. The 12-month clinical outcomes were assessed by the fire-walled DMC, and as expected the data did not yet reach statistical significance, but demonstrated a trend in clinical outcomes favoring AT-007 vs. placebo. A safety analysis showed that AT-007 continued to be safe and well tolerated. The Company is exploring a potential submission for conditional approval based on existing data with the European Medicines Agency (EMA).

AT-007 is also being studied in a rare disease caused by deficiency in the enzyme Sorbitol Dehydrogenase, called SORD Deficiency. AR is the first enzyme in the polyol pathway, converting glucose to sorbitol. AR is then followed by Sorbitol Dehydrogenase, which converts sorbitol to fructose. Patients with SORD Deficiency accumulate very high levels of sorbitol in their cells and tissues as a result of the enzyme deficiency, which results in tissue toxicities such as peripheral neuropathy and motor neuron disease. Recent research in drosophila and cell models of SORD Deficiency demonstrated that treatment with an ARI that blocks sorbitol production may provide benefit in this disease. Preclinical studies on AT-007 have demonstrated significant reduction in sorbitol levels in fibroblasts from SORD deficient patients. Treatment with AT-007 in the drosophila model of SORD prevented the disease phenotype and protected from neuronal degeneration. On October 25, 2021, we reported data from a pilot open-label study in 8 SORD Deficiency patients. AT-007 reduced blood sorbitol levels by approximately 66% from baseline through 30 days of treatment. AT-007 was safe and well tolerated in all treated patients. In December 2021, we initiated a Phase 2/3 registrational study in patients with SORD Deficiency, which is ongoing at multiple clinical sites in the US and Europe. On February 16, 2023, we announced that in a pre-specified interim analysis of the ongoing Phase 3 INSPIRE trial, AT-007 reduced sorbitol levels by a mean of approximately 52% (or approximately 16,000ng/ml) over 90 days of treatment ($p<0.001$ vs. placebo) in patients with SORD Deficiency. At baseline, the mean blood sorbitol level of SORD patients included in this interim analysis was approximately 29,000ng/ml, with a range of approximately 22,000ng/ml-38,000ng/ml. In the INSPIRE trial, a baseline cross-sectional analysis of the relationship between sorbitol level, age (or duration of disease) and clinical outcome measures demonstrated a statistically significant correlation between sorbitol level and key clinical outcome measures, including 10-meter-walk/run speed, 4-stair climb speed, and sit-to-stand test ($p<0.05$). The Company is working with the FDA to determine the appropriate regulatory path forward, as well as data required for an NDA submission, to advance AT-007 towards registration for this indication. The INSPIRE study will continue in blinded format to the 12-month interim clinical outcomes assessment. If the primary clinical outcome measure (10-meter-walk/run) reaches statistical significance at 12 months, the study will be completed and unblinded. If not, the study will continue in blinded format to 24 months, where clinical outcomes will be assessed again in a final statistical analysis. AT-007 continues to be safe and well tolerated to date.

We also plan to initiate a clinical development program on AT-007 in another pediatric rare disease, called PMM2-CDG. PMM2-CDG is a glycosylation disorder caused by deficiencies in the enzyme phosphomannomutase 2, which leads to CNS symptoms similar to Galactosemia, including low IQ, tremor, and speech and motor problems. AR is over-activated in this disease as a compensatory consequence of PMM2 deficiency, and a CNS penetrant ARI may be a compelling clinical option. Initial data in fibroblast cell lines derived from PMM2-CDG patients demonstrates that AT-007 treatment increases phosphomannomutase 2 activity. A young child with PMM2-CDG is being treated in a single-patient investigator initiated trial with AT-007 at the University of North Carolina School of Medicine. Data has been presented at medical conferences in 2022 supporting a favorable treatment effect of AT-007 on biomarkers and organ function in this patient. The FDA has granted pediatric rare disease designation and orphan designation for AT-007 in PMM2-CDG.

In January 2023 we announced a partnership with Advanz Pharma for commercialization of AT-007 (govorestat) in Europe, and entered into an Exclusive License and Supply Agreement with Advanz Pharma (the Advanz Agreement). Advanz Pharma is a pharmaceutical company with a strategic focus on commercialization of specialty, hospital, and rare disease medicines in Europe. Under the terms of the Advanz Agreement, Advanz Pharma receives exclusive commercial rights in the European Economic Area, Switzerland, and the UK for AT-007 in Galactosemia and SORD Deficiency, with certain rights to future indications for AT-007 in Europe. We will receive certain near-term development milestone payments upon clinical trial completion and marketing authorization in Europe as well as commercial sales milestones, which in the aggregate amount to over €130 million, including €10 million upfront, which was paid upon signing. We will also receive royalties on any future net sales of AT-007 in Europe of 20%. We will continue to be responsible for the development, manufacturing and supply of AT-007, and Advanz Pharma will be responsible for packaging, distribution and commercialization in Europe.

AT-001 is a novel ARI with broad systemic exposure and peripheral nerve permeability that we are developing for the treatment of diabetic cardiomyopathy, or DbCM, a fatal fibrosis of the heart, for which no treatments are available. We completed a Phase 1/2 clinical trial evaluating AT-001 in approximately 120 patients with type 2 diabetes, in which no drug-related adverse effects or tolerability issues were observed. In September 2019, we announced the initiation of a Phase 3 registrational trial of AT-001 in DbCM. The study, called ARISE-HF, is designed to evaluate AT-001's ability to improve or prevent the decline of functional capacity in patients with DbCM at high risk of progression to overt heart failure. Although we did experience enrollment delays in 2020 associated with the Covid-19 pandemic, modifications were made to the trial to include additional sites and geographies to address Covid-19-related issues. The trial is now fully enrolled with 675 patients.

AT-003 is a novel ARI designed to cross through the back of the eye when dosed orally, and has demonstrated strong retinal penetrance, for the treatment of diabetic retinopathy, or DR. DR is an ophthalmic disease that occurs in diabetic patients and for which treatments are currently limited to high-cost biologics requiring intravitreal administration. DR has been linked to AR activity, including elevations in sorbitol and subsequent changes in retinal blood vessels, which distorts vision and leads to permanent blindness.

AT-104 is a preclinical dual selective PI3K inhibitor. Due to recent regulatory changes impacting development of the PI3K inhibitor class of compounds, the Company has discontinued its early stage preclinical PI3K program and further development of AT-104. The compound and all rights associated with the technology were returned to Columbia University.

Since inception in 2016, our operations have focused on developing our product candidates, organizing and staffing our company, business planning, raising capital, establishing our intellectual property portfolio and conducting clinical trials. We do not have any product candidates approved for sale and have not generated any revenue.

We have incurred significant operating losses since inception in 2016. Our ability to generate product revenue sufficient to achieve profitability will depend on the successful development and commercialization of one or more of our product candidates. Our net loss was $82.5 million for the year ended December 31, 2022. As of December 31, 2022, we had an accumulated deficit of $348.8 million. We expect to continue to incur significant expenses and increasing operating losses for the foreseeable future in connection with our ongoing activities. Furthermore, we expect

to incur additional costs associated with operating as a public company, including significant legal, accounting, investor relations and other expenses. As of December 31, 2022, we had cash and cash equivalents and short-term investments of $30.5 million.

Our management team and scientific advisory board are composed of accomplished scientists and clinicians with decades of experience developing drugs for a wide range of diseases. Our view is that drug development does not always need to follow the standard approach, which often requires long and costly development programs before drugs become available to patients. By taking a unique and focused approach to drug development, we believe we can significantly shorten development programs and bring lifesaving drugs to patients in urgent need. In May 2019, we completed our initial public offering (the "IPO") whereby we sold 4,000,000 shares of common stock at a public offering price of $10.00 per share, resulting in aggregate net proceeds of $34.6 million, after deducting underwriting discounts and commissions and offering expenses. In November 2019, we completed a private placement of 1,380,344 shares of our common stock (the "Private Placement"), which resulted in net proceeds of approximately $18.4 million. In January 2020, we completed a secondary public offering of 2,471,489 shares of our common stock, including 411,223 shares sold pursuant to the underwriters' full exercise of their option to purchase additional shares (the "Secondary Public Offering"), pursuant to which we received $134.1 million of proceeds, net of underwriting discounts and commissions and offering expenses. In February 2021, we issued and sold 3,000,000 shares of common stock (the "February Offering") at a public offering price of $23.00 per share, with an additional 450,000 shares sold pursuant to the underwriters' full exercise of their option to purchase additional shares in the February Offering. We received aggregate net proceeds, net of underwriting discounts and commissions and offering costs of $74.4 million. In June 2022, we completed an underwritten public offering of 20,000,000 shares of our common stock, par value $0.0001 per share, 10,000,000 Pre-Funded Warrants, and accompanying Common Warrants to purchase up to 30,000,000 shares of our common stock. The shares and accompanying Common Warrants were offered at a price to the public of $1.00 per share and warrant, and the Pre-Funded Warrants and accompanying Common Warrants were offered at a price to the public of $0.9999, resulting in aggregate net proceeds of approximately $27.8 million, after deducting underwriting discounts and commissions and offering expenses.

We are actively pursuing several potential financing options. While we continue to explore opportunities to raise additional equity capital in the public markets, this has proven to be challenging in the biotech sector recently. Other options for structured finance which we continue to explore include a PIPE, debt, convertible debt, and synthetic royalty financing. Synthetic royalty financing, in particular, has become a favorable option for many companies for funding ongoing clinical development in late-stage and pre-approval programs. We have engaged an investment bank and we are specifically exploring this option in the near term. Additionally, we are in active dialogue with several potential partners regarding business development opportunities related to one or more of our programs. There can be no assurances that our discussions with any of the current counterparties will be successful, and the Company expects to continue to pursue additional opportunities.

Our Strategy

Our goal is to bring potentially transformative therapies to market across a range of fatal or debilitating diseases for which no treatments are available. The critical components of our strategy include:

- ***Leveraging our unique approach to develop our pipeline of novel ARIs.*** We target molecules and pathways that have a proven role in disease, but have previously failed to yield successful products due to poor efficacy and tolerability. Our unique approach to drug development utilizes recent technological advances to design improved drugs, employs early use of biomarkers to confirm biological activity and focuses on abbreviated regulatory pathways. We develop product candidates with increased potency and selectivity by leveraging recent technological advances in high throughput crystallography and in silico structural design. Our strategy is also informed by early use of biomarkers to confirm biological activity and target engagement. Early proof of biological activity through biomarkers in clinical trials combined with data from prior clinical development programs on first generation drugs significantly de-risks clinical development in our target indications. AR is our first molecular target that has been implicated in multiple diseases and for which sorbitol levels can be assessed as a biomarker of enzyme activity. Prior AR-targeting compounds produced nonselective inhibitors and failed to demonstrate adequate safety and

efficacy. We intend to apply our strategy to a wide range of validated targets across multiple disease indications, which we believe will result in additional pipeline programs.

- ***Rapidly advancing the development of our ARI product candidates, AT-007, AT-001 and AT-003.*** *Registrational studies for AT-007 in pediatric Galactosemia and SORD Deficiency and for AT-001 for the treatment of DbCM are ongoing.*

- ***Taking advantage of regulatory pathways designed for accelerated drug development in indications with high unmet need and seeking strategic partnerships in other indications.*** We plan to leverage abbreviated development programs and biomarker-based approaches for rapid drug development and regulatory approval where possible. For indications that require standard development programs, we plan to seek strategic partnerships.

- ***Expanding our pipeline to products targeting other validated molecules and pathways outside of AR.*** We will continue leveraging our relationships with academic institutions and universities to acquire or license additional technologies that are consistent with our strategy of applying new technologies to validated molecular pathways.

Our Pipeline

The following table shows the status of our current ARI and PI3K inhibitor programs:

Compound	Preclinical	Phase 1	Phase 2	Phase 3	Dosing	Target Tissue	Milestones	Rights
ALDOSE REDUCTASE FRANCHISE								
AT-007	Galactosemia (ACTION)				QD Oral	CNS	Positive adult and pediatric biomarker data; pediatric Phase 3 outcomes trial ongoing	ROW, ADVANZ PHARMA EU
	SORD Deficiency (INSPIRE)				Oral	CNS	Positive pilot study data; Phase 3 registrational trial ongoing	ROW, ADVANZ PHARMA EU
	PMM2-CDG				Oral	CNS	Phase 2 ready; Expanded Access open	WW
AT-001	Diabetic Cardiomyopathy (ARISE-HF)				BID Oral	Systemic	Ph 3 registrational trial data read-out YE 2023	WW
	Diabetic Peripheral Neuropathy				Oral	Peripheral Nerve	Sub-study embedded in DbCM Ph 3 trial	WW
AT-003	Diabetic Retinopathy				Oral	Retina	Phase 1 ready	WW

We seek to protect our proprietary and intellectual property position for our product candidates, our core technology, and other know-how through U.S. and foreign patent protection. To the extent that our platform is not patentable, we rely on trade secret protection and confidentiality agreements to protect our interests. For more information, see the section titled "Business — Intellectual Property."

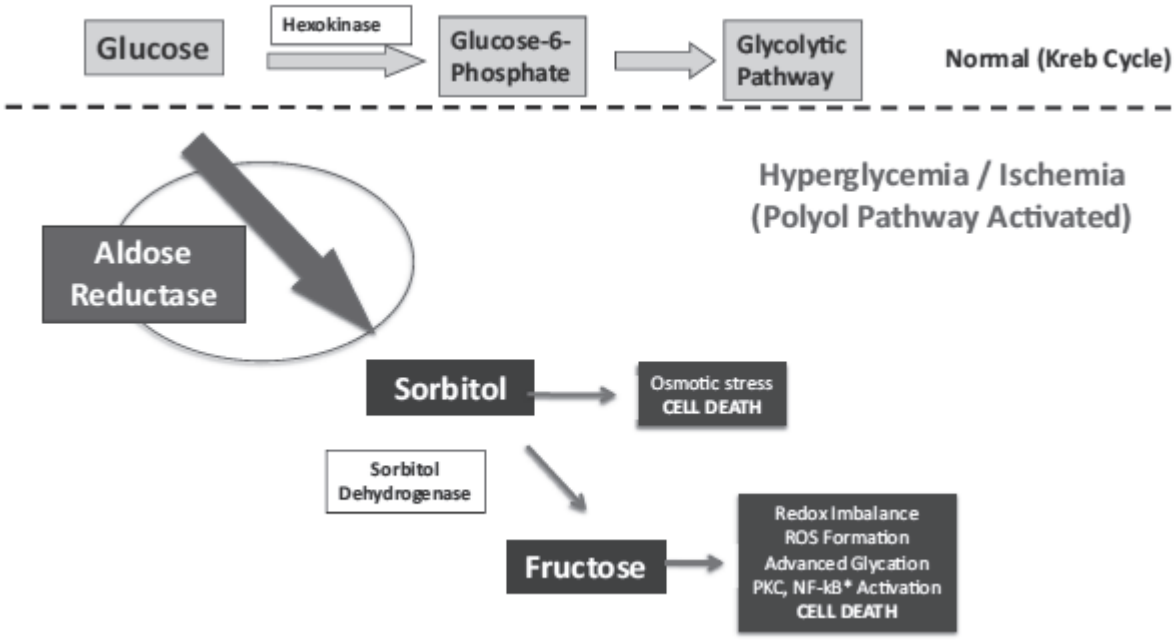
Our Product Candidates

Our Aldose Reductase Program

AR is the first enzyme and rate-limiting step in the polyol pathway, an alternative glucose metabolism pathway. AR is a redox-regulated enzyme that is activated by an altered redox state within the cell, which occurs during hyperglycemia and ischemia. AR activation is associated with downstream consequences of hyperglycemia, such as diabetic complications, as well as consequences of ischemia in the heart, such as acute myocardial infarction and chronic

heart failure. As shown in the figure below, AR activity produces excess sorbitol, which causes osmotic dysregulation within cells and tissues, such as nerve and retina, and is toxic to many cell types, including cardiomyocytes. Sorbitol is also further metabolized to fructose, which initiates a cascade of metabolic dysregulation and inflammatory damage to cells, such as: reactive oxygen species, or ROS, generation; advanced glycation end products, or AGE; protein kinase C, or PKC, activation; and methylglyoxal overproduction. Under non-oxidative, or healthy patient conditions, AR remains largely inactive and less than 3% of a healthy person's glucose is processed by the polyol pathway. However, when the oxidative environment of the cell changes due to hyperglycemia or ischemia, AR is both activated and upregulated, and greater than 30% of the patient's glucose is then shunted through the polyol pathway, resulting in significant downstream damage to cells and tissues. The detrimental consequences of AR activation have been well established by decades of prior research. These include broad effects, such as mitochondrial dysfunction and cell death, as well as tissue-specific changes, such as neuronal degeneration in peripheral nerves, collagen crosslinking and fibrosis in cardiac tissue, and damage to blood vessels in the lens of the eye.

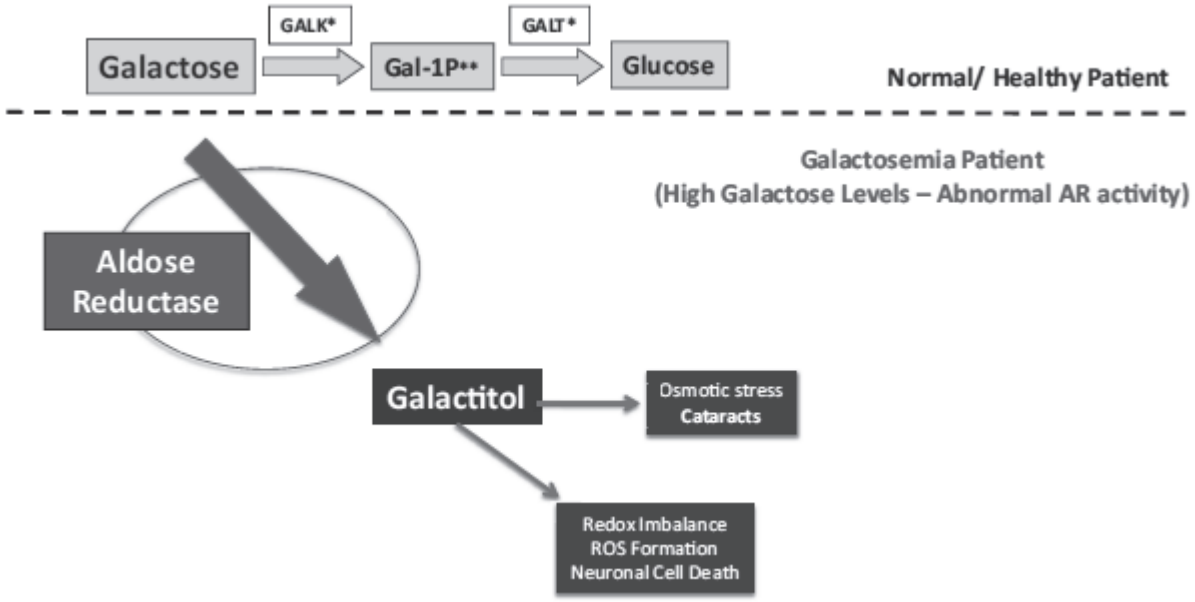
AR Causes Damage to Tissues Under Conditions of Oxidative Stress



* NF-kB is a protein complex that controls transcription of DNA, cytokine production and cell survival.

Additionally, as shown in the figure below, abnormal AR activity is associated with conversion of galactose to galactitol in patients with Galactosemia. Galactitol, like sorbitol, does not cross the cell membrane and causes damage to cells across a wide range of tissues, including neurons in the brain, retinal cells in the eye and peripheral nerve tissue.

Galactitol Accumulation Results in Tissue Specific Damage



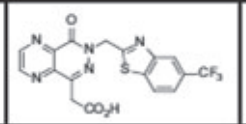
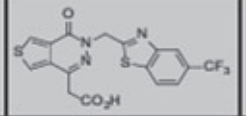
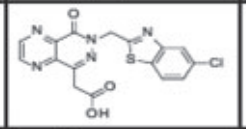
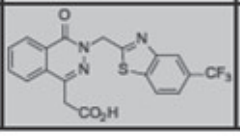
* GALK, or galactokinase, and GALT, or galactose-1-phosphate uridyl transferase, are enzymes that metabolize galactose.

** Galactose-1-phosphate is referred to as Gal-1P.

During the 1980s and 1990s, AR was a significant target of drug development due to its established role in a wide range of debilitating indications. Although these programs failed to produce effective drugs with a favorable risk/benefit profile, the prior ARI clinical development programs validated the role of AR in the pathogenesis of several diabetic complications and provided useful information on optimal patient criteria and trial design.

By applying new techniques in crystallography to better understand how the enzyme works, and applying in silico design and medicinal chemistry approaches, we have developed compounds with logarithmically improved potency and increased selectivity. Our technology includes specific compounds that are in various stages of preclinical and clinical development, and is coupled with an understanding of how the enzyme works and a knowledge base of structural approaches to drug the target while controlling drug characteristics, such as PK, solubility and tissue permeability.

The following table summarizes the current status of our AR program and compound differentiation:

Compound	Structure	IC_{50}[1]	Maximum Tolerated Dose in Animals	LogD[2]	Tissue Penetration (in rats)			
					Systemic/ Heart	Nerve	Retina	CNS
AT -001		30pM	>2,000 mg/kg	-1.00	✓	✓	✓	X
AT -007		100pM	>1,000 mg/kg	-0.09	✓	✓	✓	✓
AT -003		54pM	>1,000 mg/kg	-1.53	✓	✓	✓	X
Zopolrestat (prior Pfizer compound)		10nM	100 mg/kg	+0.06	✓	✓	X	X

(1) IC_{50} is the amount of a compound required to inhibit 50% of enzyme activity.

(2) LogD is a log of partition of a chemical compound between the lipid and aqueous phases. LogD often predicts retinal permeability, with compounds with negative LogD passing through the back of the eye.

AT-007 for the Treatment of Rare Metabolic Disease (Galactosemia, SORD Deficiency, PMM2-CDG)

Overview

AT-007 is a novel CNS penetrant ARI for the treatment of CNS rare diseases, including Galactosemia, SORD deficiency and PMM2-CDG.

Galactosemia

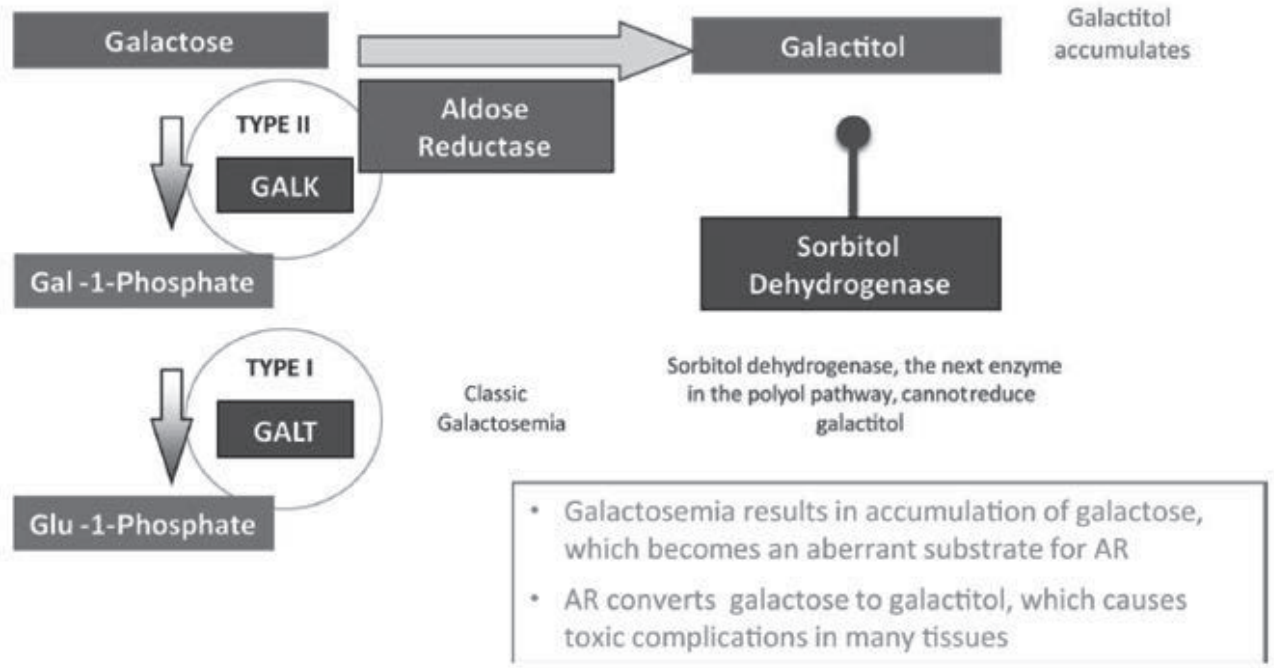
Galactosemia is a devastating rare pediatric metabolic disease that affects how the body processes a simple sugar called galactose, and for which there is no known cure or approved treatment available. High levels of galactose circulating in the blood and tissues of Galactosemia patients enable AR to convert galactose to a toxic metabolite, galactitol, which results in long-term complications ranging from CNS dysfunction to cataracts. AT-007 was specifically designed to be CNS penetrant to address AR activity in the brain and potentially prevent CNS consequences of the disease. We have demonstrated that treatment with AT-007 in an animal model of Galactosemia reduces toxic galactitol levels and prevents disease complications. We have also demonstrated that in patients with Galactosemia, plasma galactitol level statistically correlates with disease severity (p=0.004), further supporting the role of toxic galactitol in causing long-term disease complications. In adult and pediatric Galactosemia patients, we have demonstrated that AT 007 treatment resulted in a statistically significant reduction in plasma galactitol versus placebo. A pediatric long-term clinical study is underway.

Diagnosis and Standard of Care

Galactosemia is caused by severe deficiency in the GALK or GALT enzymes that metabolize galactose. Galactose is a sugar produced endogenously by the body, and is also a metabolite of lactose. Galactosemia is often fatal in infants within the first weeks of life if they are exposed to dietary lactose in the form of breast milk or dairy-based formula. As such, there is mandatory newborn screening for Galactosemia in the United States and many countries in Europe. While prompt identification of infants with Galactosemia and immediate implementation of a lactose-restricted diet prevents many fatalities, long-term consequences of disease persist due to endogenous generation of galactose within the body. We are specifically developing AT-007 for patients with severe enzyme deficiencies in GALK, which is referred to as type 2 Galactosemia, and GALT, which is referred to as classic Galactosemia. In these patients, despite dietary restriction, Galactosemia manifests as a combination of CNS and systemic toxicities in tissues, including cognitive dysfunction and intellectual deficiencies, speech and motor pathologies, pre-senile cataracts and tremor, as well as ovarian insufficiency in females.

There are no treatments available for Galactosemia. Due to endogenous production of galactose within the body, infants with Galactosemia develop significant complications even with immediate implementation of, and strict adherence to, a dairy-free diet. CNS complications include cognitive impairment, low IQ, speech and motor deficiencies, and seizures. In addition, nearly all females develop ovarian insufficiency. Further to the damage that occurs in childhood, many adults also develop persistent cataracts, seizures, and experience progressive worsening of tremor, cognitive, behavioral and psychiatric issues due to ongoing tissue deposition of galactitol.

AR Activity Causes Toxic Accumulation of Galactitol in Galactosemia



We have demonstrated that inhibiting AR activity shifts galactose metabolism to an alternative enzyme called galactose dehydrogenase, which allows galactose to be metabolized to galactonate, a benign substance that is removed in the urine.

Market Opportunity

The global incidence of Galactosemia is estimated to be 1 in 50,000 to 1 in 90,000, depending on ethnicity. The U.S. Galactosemia population is approximately 3,000 patients, based on newborn screening data identifying

2,500 infants through 2014, and the estimated birth rate of 80 patients per year. Prior studies estimated that the U.S. Galactosemia population was higher based on the incidence rates, because they did not take into account that, prior to newborn screening, most infants with Galactosemia died within a few weeks of birth. As a result, the disease prevalence is significantly lower, and the live population with Galactosemia is largely age 40 and younger. The EU population (including the UK) is slightly larger than the US population, estimated at approximately 4,000 patients, leading to a combined US + EU market opportunity of approximately 7,000 patients. When additional markets, such as Japan and Canada are considered, we believe the overall Market opportunity for Galactosemia is approximately 7,600 patients worldwide.

Preclinical Studies

A rat model of classic Galactosemia displays similar biochemical and functional abnormalities to those associated with Galactosemia in humans.

Treatment with AT-007 significantly reduced galactitol levels in target tissues, including blood, brain and liver, without increasing galactose or Gal-1P levels, and prevented complications associated with galactitol accumulation in tissues, including cataract formation and CNS dysfunction. The effects of AT-007 were dose dependent and corresponded with galactitol reduction.

Clinical Development

ACTION-Galactosemia Phase 1/2 Study

We have evaluated AT-007 in a pivotal Phase 1/2 clinical trial in healthy volunteers and adults with Galactosemia. The Phase 1 portion of the study in healthy volunteers evaluated safety, tolerability, CNS penetrance and PK of AT-007 at doses of 5mg/kg to 40mg/kg for up to seven days of consecutive treatment. The Phase 2 portion in adults with Galactosemia evaluated safety, tolerability, PK and pharmacodynamic reduction in the biomarker galactitol. Patients received AT-007 5mg/kg, 20mg/kg, 40mg/kg or placebo, for 28 days.

AT-007 treatment resulted in a statistically significant and robust reduction in plasma galactitol versus placebo in adult Galactosemia patients. Reductions in galactitol were dose dependent, with higher concentrations of AT-007 resulting in a greater magnitude of reduction in galactitol. At the higher doses tested (20mg/kg and 40mg/kg), AT-007 significantly reduced plasma galactitol by approximately 50% from baseline. Results were statistically significant (p value of less than 0.01) vs. placebo. Galactitol reduction was rapid and sustained over time. No substantial change from baseline was observed in placebo treated patients. AT-007 was well tolerated in both Galactosemia patients and healthy volunteers.

ACTION-Galactosemia Kids

In June 2020, we initiated the ACTION-Galactosemia Kids pediatric Galactosemia study. The study was placed on partial clinical hold in August 2020 while we worked with the FDA to redesign and operationally modify the study to seamless design to ensure continuous treatment and the opportunity to receive clinical benefit. The study re-started in February 2021 and is currently ongoing. The pediatric clinical trial is a 2-part study to evaluate safety, pharmacokinetics, and reduction in the toxic biomarker, galactitol (Part A), as well as impact on functional outcomes in children with Galactosemia over time (Part B). Three age cohorts are being studied in parallel: age 2-6, age 7-12, and age 13-17. An additional cohort of children under 2 years of age may be added following analysis of safety data from the initial pediatric cohorts. We have completed the biomarker portion of the study, demonstrating a 40% reduction in plasma galactitol ($p<0.001$ vs. placebo). The clinical outcomes portion of the study is ongoing, evaluating the impact of AT-007 on how patients feel and function over time.

While we had initially planned to submit an NDA for Accelerated Approval based on galactitol reduction, the FDA has since communicated that clinical outcomes data will be required for approval. The long-term functional outcomes portion of the pediatric study is ongoing, and the outcomes are assessed every 6 months by a fire-walled data monitoring committee (DMC). When the study reaches statistical significance in the active treated arm vs. the placebo

arm, the DMC will alert the Company and the trial will be unblinded. Based on discussions with the FDA, the Company believes that the pediatric study as it is currently designed would support an NDA submission if statistical significance is reached. The 12-month clinical outcomes were assessed by the fire-walled DMC, and as expected the data did not yet reach statistical significance, but demonstrated a trend in clinical outcomes favoring AT-007 vs. placebo. A safety analysis showed that AT-007 continued to be safe and well tolerated. The Company is exploring a potential submission for conditional approval based on existing data with the European Medicines Agency (EMA).

SORD Deficiency

SORD Deficiency is a newly characterized genetic cause of Charcot-Marie-Tooth Type 2 Disease ("CMT2") and distal hereditary neuropathy, in which patients are deficient in the enzyme Sorbitol Dehydrogenase ("SORD"). SORD is the enzyme which follows AR in the polyol pathway and converts sorbitol to fructose. Patients who are deficient in SORD can't metabolize sorbitol normally, and sorbitol levels accumulate to unnaturally high levels. Sorbitol, like galactitol, has been shown to be toxic to cells, especially neurons, resulting in progressive neuronal degeneration. Patients with SORD Deficiency develop progressive neuropathy, which greatly impacts mobility and motility, and significantly affects quality of life.

Diagnosis and Standard of Care

Currently, patients with SORD Deficiency are diagnosed based on neurological symptoms and confirmatory genetic testing, which is available through several commercial labs and hospital systems. There are currently no drugs approved to treat SORD Deficiency.

Market Opportunity

Genetic studies indicate that approximately 7-9% of CMT2 cases are caused by SORD Deficiency, estimating the US population around 3,300 patients. The EU population (including the UK) is estimated to be approximately 4,400 patients. When additional markets, such as Japan and Canada are considered, we believe the overall Market opportunity for Galactosemia is approximately 8,400 patients worldwide.

Preclinical Studies

Substrate reduction through AR inhibition in patient fibroblasts and a drosophila model of disease have demonstrated preclinical proof of concept in SORD Deficiency, significantly reducing sorbitol levels and normalizing the drosophila disease phenotype. Preclinical studies in fibroblasts derived from SORD Deficiency patients have demonstrated significant reduction in sorbitol levels with AT-007 treatment. Preclinical studies in the drosophila model of disease have demonstrated a positive impact on the disease phenotype with AT-007 treatment, including mobility (climbing) and prevention of neuronal degeneration.

Clinical Development

In 2021 we conducted an open-label pilot study in 8 patients with SORD Deficiency. AT-007 treatment significantly reduced sorbitol levels by approximately 66% from baseline, and was safe and well tolerated. In December 2021 we initiated a Phase 2/3 registrational study in patients with SORD Deficiency. The registrational study, called the INSPIRE trial, is designed to demonstrate biomarker efficacy at 3 months through reduction in sorbitol, and long-term clinical efficacy over 2 years of treatment, with an interim clinical outcomes assessment at 12 months. The study is a multicenter placebo controlled trial conducted in the US and Europe in approximately 50 SORD patients age 16 and older. On February 16, 2023, we announced that in a pre-specified interim analysis of the ongoing Phase 3 INSPIRE trial, AT-007 reduced sorbitol levels by a mean of approximately 52% (or approximately 16,000ng/ml) over 90 days of treatment ($p<0.001$ vs. placebo) in patients with SORD Deficiency. At baseline, the mean blood sorbitol level of SORD patients included in this interim analysis was approximately 29,000ng/ml, with a range of approximately 22,000ng/ml-38,000ng/ml. In the INSPIRE trial, a baseline cross-sectional analysis of the relationship between sorbitol level, age (or duration of disease) and clinical outcome measures demonstrated a statistically significant correlation between sorbitol level and key clinical outcome measures, including 10-meter-walk/run speed, 4-stair climb speed, and sit-to-stand test

($p<0.05$). The Company is working with the FDA to determine the appropriate regulatory path forward, as well as data required for an NDA submission, to advance AT-007 towards registration for this indication. The INSPIRE study will continue in blinded format to the 12-month interim clinical outcomes assessment. If the primary clinical outcome measure (10-meter-walk/run) reaches statistical significance at 12 months, the study will be completed and unblinded. If not, the study will continue in blinded format to 24 months, where clinical outcomes will be assessed again in a final statistical analysis. AT-007 continues to be safe and well tolerated to date.

PMM2-CDG

PMM2-CDG is a glycosylation disorder in which patients have only partial function of the phosphomannomutase enzyme ("PMM2"). As a result, patients do not process sugars properly to support protein glycosylation, which results in systemic problems and multi-organ failure. PMM2-CDG is a severe disease, resulting in and high mortality in children, with no FDA approved treatments. PMM2-CDG is an ultra-rare disease, with only approximately 1,000 patients identified worldwide.

Recently, AR inhibition was demonstrated to positively impact protein glycosylation in PMM2-CDG patient fibroblasts and a C. elegans model of disease. It is believed that AR inhibition results in increased protein glycosylation by shifting the balance of sugar production to support PMM2 activity. In preclinical studies in PMM2-CDG patient fibroblasts, AT-007 significantly improved PMM2 activity. Based on this data, we have received both Orphan Designation and Pediatric Rare Disease designation from the FDA.

AT-001 for the Treatment of Diabetic Cardiomyopathy

Overview

We are developing AT-001, a novel ARI with broad systemic exposure and peripheral nerve permeability being developed for the treatment of DbCM, a fatal fibrosis of the heart, for which no treatments are available. We completed a Phase 1/2 clinical trial evaluating AT-001 in approximately 120 patients with type 2 diabetes, in which no drug-related adverse effects or tolerability issues were observed. This trial also demonstrated target engagement and proof of biological activity, as measured by reduction in sorbitol, a biomarker of AR activity and NTproBNP. A registrational Phase 2/3 study in DbCM patients at high risk of progression to overt heart failure (ARISE-HF) is currently ongoing.

Diagnosis and Standard of Care

DbCM is a fatal fibrosis of the heart that occurs in both type 1 and type 2 diabetic patients, which leads to decreased contractility and decreased heart function, eventually resulting in fulminant heart failure. DbCM is caused by metabolic derangements in cardiomyocytes that result in cell death and fibrosis. AR activity has been shown to be a large contributor to these metabolic derangements, and the downstream effect of AR activation is responsible for the cardiomyocyte cell death and fibrosis. DbCM is diagnosed by increased weight of the heart and decreased contractility, which are identified by echocardiographic screening, as well as by exclusion of other forms of heart disease. Epidemiological studies have shown that approximately 17% to 24% of diabetic patients display DbCM in the absence of any other forms of heart disease. These patients do not have hypertension, atherosclerosis, valvular heart disease or ischemia, and the only cause of the cardiomyopathy is the underlying diabetes. Stages of DbCM range from asymptomatic, or stage 1, to acute heart failure, or stage 4. Most patients are not diagnosed until stage 2, where symptoms manifest as extreme shortness of breath during exercise, referred to as decreased exercise tolerance. Exercise tolerance in these patients (as measured by maximum amount of oxygen a person can utilize during intense exercise known as peak VO2) is approximately 25% lower than diabetic patients without DbCM, and decreases by an additional 30% as the patients progress to overt heart failure in later stages of diseases. Patients quickly progress at a steady state of decline to stage 3, which includes marked cavity dilation and severe limitations in daily activities. The final stage of DbCM, stage 4, is represented by acute heart failure resulting in death. The current standard of care is to target glucose control in these patients, as well as hemodynamic modulation of blood flow, through use of beta blockers and diuretics. Both approaches are largely ineffective, and DbCM often results in death within five to ten years of diagnosis. Approximately 24% of DbCM patients progress to overt heart failure or death within 1.5 years of diagnosis, and 37% within five years of diagnosis.

Market Opportunity

According to a retrospective epidemiological study, approximately 17% of patients suffering from diabetes develop DbCM. A study completed in France that utilized echocardiographic screening estimates the proportion of diabetic patients to develop DbCM at approximately 24%. The International Diabetes Foundation estimated that there were approximately 451 million patients globally with diabetes in 2017, which is expected to increase to 693 million by 2045. This includes 58.0 million diabetes patients in Europe in 2017, which is expected to increase to 67.0 million in 2045, and 46.0 million in North America, which is expected to increase to 62.0 million in 2045. Based on an estimated prevalence of 17% of diabetic patients who develop DbCM, we estimate that currently there are approximately 77.0 million patients with DbCM globally, with approximately 8.0 million in North America and 10.0 million in Europe. Initially, our development program will target patients at high risk of progression to overt heart failure, which we estimate constitute approximately 50% of all DbCM patients. We believe these patients represent a symptomatic population that is more likely to be responsive to treatment.

Prior AR-Based Approaches to Treat DbCM

AR activity has been implicated as a strong contributing factor to pathogenesis in DbCM. Pfizer Inc. was developing an ARI, Alond (zopolrestat), for the treatment of DPN and DbCM in a Phase 2 clinical trial that demonstrated favorable outcomes on heart function in DbCM patients, but the clinical trial was discontinued due to an unfavorable risk/benefit profile, with several patients experiencing liver toxicity and significant elevations in both aspartate aminotransferase and alanine aminotransferase, which are enzymes central to identification of liver toxicity and damage. In this trial, patients with early-stage DbCM were identified by echocardiographic screening and were randomized to three treatment groups, which consisted of placebo, 500 mg zopolrestat per day or 1,000 mg zopolrestat per day dosed for one year. Due to liver toxicity seen in another trial with zopolrestat, the 1,000 mg treatment arm was reduced to 500 mg, and the two doses were collapsed into one treatment arm. While patients on placebo displayed decreased heart function over the year of the trial as their disease progressed, patients on zopolrestat displayed a stabilization of heart function and even improvement in heart function in some patients based on hemodynamic endpoints. We believe this data validates the approach of using an ARI to improve outcomes for patients with DbCM and using our compounds, which demonstrate improved potency and have been well tolerated, may lead to greater clinical utility.

We have demonstrated that when compared to zopolrestat, AT-001 has significantly higher in vitro enzymatic inhibitory activity and greater specificity for AR. Liver toxicity associated with “old” ARIs such as zopolrestat has been shown to be due to off-target inhibition of a structurally related enzyme, Aldehyde Reductase, which is required for normal liver function. AT-001 demonstrates increased selectivity for AR, and does not inhibit Aldehyde Reductase at any concentration tested. This increased selectivity led to lack of toxicity in cultured hepatocytes, or liver cells, whereas zopolrestat demonstrated significant toxicity in hepatocytes. Thus, we believe that not only is AT-001 a more potent AR inhibitor than prior drugs, but that we have overcome the safety and toxicity limitations from prior compounds, which were due to lack of selectivity and off-target inhibition of Aldehyde Reductase.

Preclinical Efficacy Studies

In a preclinical model of DbCM AT-001 prevented cardiac damage and dysfunction and normalized cardiac energetics. In a diabetic rat model, AT-001 prevented cardiac damage induced by ischemia/repurfusion.

Clinical Development

Until recently, development in cardiovascular disease indications often required large outcome-based trials that examined survival and re-hospitalization as primary endpoints. These trials were extremely large, expensive and time-consuming, and were often confounded by comorbidities in the patient population. As a result, very few cardiovascular programs resulted in approved drugs. There has been a recent effort from the Division of Cardiovascular and Renal Products at the FDA, as well as at the European Medicines Agency, or EMA, to streamline drug development for cardiovascular disease to increase the probability of demonstrating a meaningful clinical effect in patients. Specifically, in cardiomyopathies, where there is a direct functional link between hemodynamic endpoints, heart

contractility and quality of life, there is a unique opportunity to demonstrate benefit of therapy in a smaller number of patients and shorter treatment period than was previously required. Recent clinical development programs in hereditary cardiomyopathies have pioneered smaller trials examining exercise tolerance and/or heart functional capacity as a primary endpoint.

Consistent with these developments, at our pre-IND meeting, the FDA indicated that we would not be required to examine survival and re-hospitalization endpoints, and confirmed that exercise tolerance would qualify as an appropriate primary endpoint in our DbCM trial. This was also recently publicly confirmed by the FDA in a whitepaper entitled "Draft Guidance for Industry: Treatment for Heart Failure: Endpoints for Drug Development." Accordingly, we designed our pivotal Phase 2/3 clinical trial to target functional capacity, or exercise tolerance, as measured by Peak VO2 on Cardiopulmonary Exercise Testing (CPET) in DbCM patients at high risk of progression to overt heart failure.

Phase 1/2 Trial in Adult Type 2 Diabetic Patients

We have evaluated AT-001 in a placebo-controlled Phase 1/2 clinical trial in approximately 120 type 2 diabetes patients. The primary objectives of this trial were to explore the safety, tolerability and PK profile of AT-001. Because AR converts glucose to sorbitol, and AR activity is elevated in diabetic patients, sorbitol normalization was also examined as a pharmacodynamic, or PD, biomarker of target engagement, which provided proof of biological activity in patients.

The Phase 1/2 clinical trial allowed use of concomitant treatments for glucose control, as well as other standard of care treatments for diabetes, such as statins and ACE inhibitors. The FDA permitted us to directly evaluate diabetic patients due to positive data from the preclinical studies, as well as the urgency to develop drugs quickly due to high unmet need. AT-001 was dosed as an active pharmaceutical ingredient, or API, powder in a rapid release capsule and the trial examined both once-daily and twice-daily, or BID, dosing regimens.

AT-001 was safe and well tolerated at all doses tested. Additionally, there were no observed adverse interactions with any concomitant diabetes medications used by patients during the trial. Because AR converts glucose to sorbitol, and AR activity is elevated in diabetic patients, sorbitol normalization to healthy subject levels can be used as a PD biomarker of target engagement and proof of biological activity. Treatment with AT-001 normalized sorbitol levels in diabetic patients to those of healthy volunteers, and prevented post-prandial elevations in sorbitol. Decrease in sorbitol levels was dose-dependent, with higher doses of AT-001 resulting in greater reduction in sorbitol levels. Reduction in sorbitol levels lasted for approximately 10-12 hours post dose, suggesting that twice-daily oral dosing produced optimal pharmacodynamic impact. Placebo-treated patients did not demonstrate any reduction in sorbitol levels, and conversely demonstrated post-prandial increase in sorbitol levels.

Within the Phase 1/2 study, approximately 30 patients with early stage DbCM, assessed by echocardiographic abnormalities and elevations in the cardiac stress biomarker, NTproBNP, were treated with AT-001 or placebo for 28 days. Treatment with AT-001 (twice daily or three times daily) resulted in sustained reduction in sorbitol, and significant reduction in NTproBNP, demonstrating that inhibition of AR decreases cardiac stress. This data supported dose selection and advancement into a Phase 2/3 registrational trial for DbCM.

In September 2019, we initiated a Phase 3 registrational trial for AT-001 in DbCM called ARISE-HF. ARISE-HF is a global study, recruiting patients at sites in North America, Europe, Australia and Hong Kong. The primary endpoint of the trial is stabilization or decrease in slope of decline on functional capacity, as measured by peak VO2, the rate of oxygen consumption measured during exercise. We are also evaluating heart function by echocardiogram-based hemodynamic endpoints, progression to overt heart failure, and quality of life, as well as biomarkers of heart inflammation and damage. This trial consists of 675 patients in three cohorts of approximately 225 patients each, including a placebo group, a low dose AT-001 group (1,000mg twice daily) and a high dose AT-001 group (1,500mg

twice daily). The trial treatment period for evaluation of the primary endpoint is 15 months, with additional endpoints evaluated at 27 months. The trial is fully enrolled and ongoing.

AT-001 for the Treatment of Diabetic Peripheral Neuropathy

Overview

We also intend to develop AT-001 for DPN, a debilitating neurodegenerative disease that significantly reduces patients' quality of life, and for which there are currently no FDA-approved treatments. We expect this indication will require a standard clinical development path, and as such we plan to pursue a strategic partnership in order to expand into this indication. Since many patients with DbCM also have DPN, we are collecting proof-of-concept data through our DbCM program to support our efforts in our DPN program. We have included a DPN sub-study in our pivotal DbCM study.

Diagnosis and Current Standard of Care

DPN is diagnosed by a simple neurological assessment, usually the Toronto Neuropathy Scoring System, which is administered in the physician's office and examines a patient's ability to feel various types of neurological stimuli on the hands and feet. AR activity has been shown to cause DPN. Epalrestat, an ARI, is approved in Japan, China and India to prevent further neuronal degeneration in DPN patients. However, there are no disease modifying therapies approved in the United States and Europe, and only symptomatic medications, such as Lyrica, are approved for pain associated with DPN. Although epalrestat was approved in Japan in 1992 based on very limited clinical data that would not have been sufficient for other markets, more recent academic studies have demonstrated an effect on MNCV and symptomatic pain endpoints in a wide range of diabetic patients. For example, a multicenter, three-year Phase 3 clinical trial conducted in Japan on epalrestat 150 mg versus placebo demonstrated that epalrestat prevented progression of DPN in diabetic patients versus placebo. Epalrestat prevented degeneration of nerve function, as measured by MNCV, and prevented worsening of symptomatic pain. A statistically significant effect was demonstrated in all patients regardless of low or high levels of glucose attached to their hemoglobin, as tested by a hemoglobin A1C (HbA1C) test.

Epalrestat, which is now generic in Japan, reached peak sales of approximately $226 million in 2001. This is indicative of its widespread use in the Japanese diabetic population, which was approximately five million patients at the time of launch despite significant tolerability issues associated with use and five times daily dosing due to a very short half-life. We do not believe, however, that it is likely to be a candidate for further commercialization. Nevertheless, prior research on epalrestat evinces the role of AR in DPN and provides a clinical trial design to demonstrate efficacy in this indication.

Market Opportunity

Approximately 50% of the global diabetic population, or 226 million diabetic patients, suffer from DPN, with 23.0 million patients in North America and 29.0 million patients in Europe. Due to availability of generic epalrestat in China and India, we view the opportunity in these two markets to be limited as a result of pricing pressures and differentiation requirements with regard to epalrestat. However, we believe a significant market opportunity for a more effective ARI with a favorable dosing regimen still exists in Japan, a less price sensitive market where there is familiarity with the mechanism of action in the disease and use of epalrestat is high. As such, although we are currently focused on the U.S. market, we may expand our efforts into Japan opportunistically.

Preclinical Studies

In preclinical studies, AT-001 prevented neuronal degeneration in animal models of DPN, as measured by MNCV in sciatic and tail nerves of diabetic rats. AT-001 treatment prevented peripheral neuronal damage, as measured by MNCV after six weeks of treatment. A dose-dependent reduction in neuronal dysfunction was observed in rats treated

with AT-001, and treatment at 30 mg/kg of AT-001 completely prevented neuronal degeneration, with no statistical difference from non-diabetic WT rats.

Clinical Development

Since many DbCM patients often also suffer from DPN, we have incorporated DPN endpoints, such as MNCV, as a sub-study into our DbCM ARISE-HF pivotal study to provide additional proof-of-concept for AT-001 in DPN. We plan to seek a strategic partnership to develop AT-001 for treatment of DPN and advance the program into Phase 3 clinical trial for this indication.

AT-003 for the Treatment of Diabetic Retinopathy

Overview

We are developing AT-003, an ARI designed to cross through the back of the eye when dosed orally, which has demonstrated strong retinal penetrance, for the treatment of DR. DR is an ophthalmic disease that occurs in diabetic patients, and for which treatments are currently limited to intravitreal administration. DR has been linked to AR activity, including elevations in sorbitol and subsequent changes in retinal blood vessels, which distorts vision and leads to permanent blindness. We are currently in late stages of preclinical development and intend to advance AT-003 into a Phase 1 clinical trial for the treatment of DR.

Diagnosis and Current Standard of Care

DR is diagnosed by routine dilated eye exam by an ophthalmologist. Annual or biennial ophthalmic exams to screen for DR are a recommended standard of care for diabetic patients under current treatment guidelines. Vascular endothelial growth factor, or VEGF, inhibitors, Lucentis (ranibizumab) and Eylea (aflibercept), are approved to treat severe or late-stage DR, but are limited by high cost, the need for intravitreal injection into the eye and the lack of therapeutic benefit in many patients. A need exists for safe, effective and tolerable treatments for DR early in the disease process that provide a benefit to a wide range of patients. AR is an attractive target for DR drug development since AR activity is upstream of VEGF activity in DR pathogenesis. AR has been shown to cause DR by inducing hyperosmolarity in retinal cells due to elevated sorbitol, as well as through fructose-mediated detrimental downstream effects, such as AGE generation and PKC activation. AR knock-out rats are protected from DR development, and several prior ARIs demonstrated efficacy on DR endpoints in clinical trials, but were not approved due to dose-limiting safety concerns.

Market Opportunity

A recent retrospective epidemiological analysis of diabetic patients globally confirmed that DR affects approximately 35% of diabetics, and is a leading cause of blindness worldwide. Based on the 2017 diabetes numbers, the global market for DR is approximately 158 million patients, with anticipated increase to 243 million by 2045. The current market is approximately 16.0 million in North America and 20.0 million in Europe.

Preclinical Studies

AT-003 displayed significant retinal penetration when dosed orally in diabetic rats. AT-003 was observed to be well tolerated over a seven-day dosing period in all doses tested, up to 1,000 mg/kg daily, with no adverse effects observed. Efficacy of AT-003 is currently being explored in two animal models of DR — an ischemic injury model (acute damage) and chronic diabetic treatment model.

Clinical Development Plan

Similar to AT-001, we plan to explore the safety, tolerability, PK profile and biomarker effects of AT-003 in a Phase 1a/1b clinical trial in diabetic patients. Assuming positive data in this trial, we plan to initiate a pivotal Phase 2/3 clinical trial of AT-003 in patients with DR to prevent disease progression versus placebo, as measured by subjective

metrics, including fluoroscein angiography and optical coherence tomography, which are scans used in the examination and management of retinal diseases.

Exclusive License Agreement with Columbia University

On October 26, 2016, we entered into a license agreement with Columbia University (the "2016 Columbia Agreement"). Pursuant to the 2016 Columbia Agreement, Columbia University granted us a royalty-bearing, sublicensable license that is exclusive with respect to certain patents, and non-exclusive with respect to certain know-how, in each case to develop, manufacture, and commercialize ARI products, including AT-001, AT-003 and AT-007. The license grant is worldwide with the exception of a single patent family covering AT-001 and AT-003 for which the license grant excludes China, Taiwan, Hong Kong and Macao. Under the 2016 Columbia Agreement, we are obligated to use commercially reasonable efforts to research, discover, develop and market licensed products for commercial sale in the licensed territory, and to comply with certain obligations to meet specified development and funding milestones within defined time periods. Columbia University retains the right to conduct, and grant third parties the right to conduct, non-clinical academic research using the licensed technology; *provided* that such research is not funded by a commercial entity or for-profit entity or results in rights granted to a commercial or for-profit entity. As the technology licensed to us under the 2016 Columbia Agreement was developed as a result of a U.S. government grant, the licenses granted to us under the agreement are subject to the terms of such grant, and to standard rights of the U.S. government under the Bayh-Dole Act, including the grant to the government of a non-exclusive, worldwide, freedom to operate license under any patents, and the requirement, absent a waiver, to manufacture products substantially in the United States.

As consideration for entering into the 2016 Columbia Agreement, we made a nominal upfront payment to Columbia University and, following the occurrence of certain trigger events, issued to Columbia University shares equal to 5% of our outstanding common stock on a fully diluted basis at the time of issuance. We will be required to make further payments to Columbia University of up to an aggregate of $1.3 million for the achievement of specified development and regulatory milestones, and up to an aggregate of $1.0 million for the achievement of a specified level of aggregate annual net sales, in each case in connection with products covered by the 2016 Columbia Agreement. We will also be required to pay tiered royalties to Columbia University in the low- to mid-single digit percentages on our, our affiliates' and our sublicensees' net sales of licensed products, subject to specified offsets and reductions. In addition, we are required to make specified annual minimum royalty payments to Columbia University in the mid six figures beginning on the 10th anniversary of the effective date of the agreement. When we grant sublicenses under the 2016 Columbia Agreement we are required to pay to Columbia University a portion of the net sublicensing revenue received from such third parties, at percentages between 10% and 20%, depending on the stage of development at the time such revenue is received from such third parties. The Advanz Agreement includes a sublicense under the 2016 Columbia Agreement.

Columbia University is responsible for the prosecution and maintenance of the licensed patents, in consultation with us, and subject to a requirement to give due consideration to our comments, at our expense. We have the first right, but not the obligation, to control the enforcement of licensed patents exclusively licensed to us against third parties. We are required to indemnify Columbia University for any third party claims that arise from or relate to the 2016 Columbia Agreement.

The 2016 Columbia Agreement will terminate upon the expiration of all our royalty payment obligations in all countries. We may terminate the 2016 Columbia Agreement for convenience upon 90 days' written notice to Columbia University. At its election, Columbia University may terminate the 2016 Columbia Agreement, or convert the licenses granted to us into non-exclusive, non-sublicensable licenses, in the case of (a) our uncured material breach upon 30 days' written notice (which shall be extended to 90 days if we are diligently attempting to cure such material breach), (b) our failure to achieve the specified development and funding milestone events, or (c) our insolvency. The 2016 Columbia Agreement may not be assigned by us without Columbia University's consent, except to any successor to all or substantially all of our business to which the 2016 Columbia Agreement relates and upon notice to Columbia University.

In January 2019, we entered into a second license agreement with Columbia University (the "2019 Columbia Agreement"). Pursuant to the 2019 Columbia Agreement, Columbia University granted us a royalty-bearing, sublicensable license that is exclusive with respect to certain patents, and non-exclusive with respect to certain know-how, in each case to develop, manufacture and commercialize PI3k inhibitor products. The license grant is worldwide. Under the 2019 Columbia Agreement, we are obligated to use commercially reasonable efforts to research, discover, develop and market licensed products for commercial sale in the licensed territory, and to comply with certain obligations to meet specified development and funding milestones within defined time periods. Columbia University retains the right to conduct, and grant third parties the right to conduct, non-clinical academic research using the licensed technology; provided that such research is not funded by a commercial entity or for-profit entity or results in rights granted to a commercial or for-profit entity. As consideration for entering into the 2019 Columbia Agreement, we made a nominal upfront payment to Columbia University. We will be required to make further payments to Columbia University of up to an aggregate of $1.3 million for the achievement of specified development and regulatory milestones, and up to an aggregate of $1.0 million for the achievement of a specified level of aggregate annual net sales, in each case in connection with products covered by the 2019 Columbia Agreement. We will also be required to pay tiered royalties to Columbia University in the low- to mid-single digit percentages on our, our affiliates' and our sublicensees' net sales of licensed products, subject to specified offsets and reductions. In addition, we are required to make specified annual minimum royalty payments to Columbia University, which is contingent upon the approval of the licensed products, in the mid-six figures beginning on the tenth anniversary of the effective date of the 2019 Columbia Agreement.

In July 2022, following regulatory changes impacting development of the class of PI3k inhibitors and the Company's decision to discontinue its early stage preclinical PI3k program, the Company and Columbia entered into an agreement terminating the 2019 Columbia Agreement (the "2022 Columbia Termination Agreement") as of July 25, 2022. Under the terms of the 2022 Columbia Termination Agreement, the Company assigned certain regulatory documents regarding the preclinical PI3k inhibitor AT-104 to Columbia and granted Columbia a non-exclusive royalty free license (with rights to sublicense any future Columbia licensee) under certain know-how, technical information and data relating to AT-104 that was developed by the Company during the term of the 2019 Columbia Agreement.

In March 2019, and in connection with the 2016 Columbia Agreement, the Company entered into a research services agreement (the "2019 Columbia Research Agreement") with Columbia University with the purpose of analyzing structural and functional changes in brain tissue in an animal model of Galactosemia, and the effects of certain compounds whose intellectual property rights were licensed to the Company as part of the 2016 Columbia Agreement on any such structural and functional changes. The 2019 Columbia Research Agreement had a term of 12 months from its effective date and expired in accordance with its terms.

On October 3, 2019, and in connection with the 2019 Columbia Agreement, the Company entered into a research services agreement (the "PI3k Columbia Research Agreement" and collectively with the 2016 Columbia Agreement, 2019 Columbia Agreement and 2019 Columbia Research Agreement, the "Columbia Agreements") with Columbia University with the purpose of analyzing PI3k inhibitors for the treatment of lymphoid malignancies. The PI3k Columbia Research Agreement had a term of 18 months from its effective date and expired in accordance with its terms.

License Agreement with University of Miami

On October 28, 2020, we entered into a license agreement (the "2020 Miami License Agreement") with the University of Miami relating to certain technology that is co-owned by the University of Miami (UM), the University of Rochester (UR) and University College London (UCL Business Ltd. (UCL)). UM was granted an exclusive agency from UR and UCL to license each of their rights in the technology. Pursuant to the 2020 Miami License Agreement, UM, on behalf of itself and UR and UCL, granted us a royalty-bearing, sublicensable license that is exclusive with respect to certain patent applications and patents that may grant from the applications, and non-exclusive with respect to certain know-how, in each case to research, develop, make, have made, use, sell and import products for use in treating and/or detecting certain inherited neuropathies, in particular those caused by mutation in the sorbitol dehydrogenase (SORD) gene. The license grant is worldwide. Under the 2020 Miami License Agreement, we are obligated to use commercially reasonable efforts to develop, manufacture, market and sell licensed products in the licensed territory, and to comply with certain obligations to meet specified development milestones within defined time periods. UM retains for itself UR

and UCL the right to use the licensed patent rights and licensed technology for their internal non-commercial educational, research and clinical patient care purposes, including in sponsored research and collaboration with commercial entities. As the technology licensed to us under the 2020 Miami License Agreement was developed as a result of a U.S. government grant, the licenses granted to us under the agreement are subject to the terms of such grant, and to standard rights of the U.S. government under the Bayh-Dole Act, including the grant to the government of a non-exclusive, worldwide, freedom to operate license under any patents, and the requirement, absent a waiver, to manufacture products substantially in the United States.

Under the terms of the 2020 Miami License Agreement, we are obligated to pay the University an up-front non-refundable license fee of $1.1 million, and a second non-refundable license fee of $0.5 million due on the first anniversary of the date of the license. We will be required to make further payments to UM of up to an aggregate $2.2 million for the achievement of specified patenting and development milestones, and up to an aggregate of $4.1 million for achievement of late stage regulatory milestones. We will also be required to pay royalties ranging from 0.88% - 5% on ours, our affiliates' and our sublicensees' net sales of licensed products. When we sublicense the rights granted under the 2020 Miami License Agreement to one or more third parties, we are required to pay to UM a portion of the non-royalty sublicensing revenue received from such third parties ranging from 15% – 25%. The Advanz Agreement includes a sublicense under the 2020 Miami License Agreement.

The 2020 Miami License Agreement terminates upon the expiration of all issued patents and filed patent applications or 10 years after the first commercial sale of the last product or process for which a royalty is due, unless earlier terminated. In addition, the 2020 Miami License Agreement may be terminated by us at any time upon 60 days prior written notice to UM, and may be terminated by either us or UM upon material breach of an obligation if action to cure the breach is not initiated within 60 days of receipt of written notice.

On October 28, 2020, we entered into an option agreement with the University of Miami (the "2020 Miami Option Agreement") concerning certain research activities and technology relating to SORD neuropathy that may be pursued and developed by UM. Under the 2020 Miami Option Agreement, if UM conducts such research activities, then UM is obligated to grant us certain option rights to access and use the research results and to obtain licenses to any associated patent rights upon us making specified payments to UM within specified time limits. If we elect to obtain option rights, we will be required to make payments to UM in the low-six figures to the low-seven figures, depending upon the rights we elect to obtain, and we will be obligated to make certain milestone payments in the high-six figures to mid-seven figures if UM conducts and completes certain research activities within specified time periods and we elect to receive rights to use the results of that research.

On December 14, 2020, we entered into a research agreement with the University of Miami (the "2020 Miami Research Agreement"), pursuant to which the University of Miami agreed to conduct a research study relating to SORD neuropathy and deliver a final report on the study to us. The term of the research agreement was from December 14, 2020 through December 30, 2021. The consideration for the 2020 Miami Research Agreement was $0.3 million. Due to COVID-19 pandemic disruptions certain research under the 2020 Miami Research Agreement was not completed. In January 2022, we amended the 2020 Miami Research Agreement to extend the term of the agreement to August 31, 2022.

License Agreement with Advanz Pharma

On January 3, 2023, we entered into an Exclusive License and Supply Agreement (the " Advanz Agreement") with Mercury Pharma Group Limited (trading as Advanz Pharma Holdings). Pursuant to the Agreement, we granted Advanz Pharma the exclusive right and license to commercialize drug products containing AT-007 (also known as govorestat), our proprietary Aldose Reductase Inhibitor (ARI) (the "Licensed Product"), for use in treatment of Sorbitol Dehydrogenase Deficiency ("SORD") and Galactosemia (each a "Licensed Indication") in the European Economic Area, Switzerland and the United Kingdom (the "Territory"). We also granted Advanz Pharma a right of negotiation and "most-favored nation" rights with respect to acquiring the European commercialization rights for any additional indications for which the Licensed Product may be developed in the future (or any other products we may develop solely to the extent used for the Licensed Indications).

Advanz Pharma is required to use commercially reasonable efforts to launch and commercialize the Licensed Products in the major markets in the Territory in each Licensed Indication following, and subject to, receipt of marketing authorization therein. Under the Advanz Agreement, Advanz Pharma agreed to pay us (i) an upfront payment of EUR 10 million (approx. USD $10.7 million), and certain development milestone payments upon clinical trial completions and receipt of marketing authorization in the territory, as well as certain commercial milestone payments, totaling EUR 134 million (approx. USD $142.2 million) in the aggregate, and (ii) royalties of 20% of net sales of the Licensed Product. Such royalty rate will be payable on a country-by-country basis until the later of (i) the expiration of the licensed patents covering the composition of matter of AT-007, or (ii) 10 years after the European Medicines Agency's grant of marketing authorization for the Licensed Product. The royalties are subject to certain deductions, including certain secondary finishing costs, certain step-in establishment costs and a portion of fees for any potential third party patent licenses if applicable in the future. Following the initial term of the license, as described above, the royalty rate shall be reduced to 10% and shall continue in perpetuity unless the Agreement is terminated in various circumstances in accordance with its terms.

Certain of the patents licensed to Advanz Pharma under the Advanz Agreement are sub-licensed from the University of Miami and Columbia University, and thus remain subject to certain obligations of the Company (including royalty obligations) to such institutions. For more information on these arrangements see "—Exclusive License Agreement with Columbia University" and "—License Agreements with the University of Miami."

Sales and Marketing

Due to the delay in the anticipated Galactosemia commercial launch, external non-essential commercial expenditures have been suspended, including sales and marketing, and we have recognized significant reductions in our commercial spending during the year ended December 31, 2022.

Manufacturing

We do not own or operate, and currently have no plans to establish, any manufacturing facilities. We depend on third party contract manufacturing organizations, or CMOs, for all of our requirements of raw materials, drug substance and drug product for our preclinical research and our clinical trials for AT-007, AT-001 and AT-003. We have not entered into long-term agreements with our current CMOs. We intend to continue to rely on CMOs for later-stage development and commercialization of our current products, as well as the development and commercialization of any other product candidates that we may identify. Although we rely on CMOs, we have personnel and third party consultants with extensive manufacturing experience to oversee the relationships with our contract manufacturers.

We believe the synthesis of the drug substance for AT-007 and AT-001 are reliable and reproducible from readily available starting materials, and the synthetic routes are amenable to large-scale production and do not require unusual equipment or handling in the manufacturing process. We have obtained adequate supplies of the drug substance for AT-007 and AT-001 to satisfy our immediate clinical and preclinical demands.

Drug product formulation development for AT-007 and AT-001 are in progress. We have contracted with a third party manufacturer capable of both formulation development and drug product manufacturing through commercialization. We may identify a second drug product manufacturer in the future to add additional capacity and redundancy to our supply chain.

Competition

The pharmaceutical industry is characterized by rapidly advancing technologies, intense competition and a strong emphasis on proprietary products. While we believe that our technology, the expertise of our executive and scientific team, research, clinical capabilities, development experience and scientific knowledge provide us with competitive advantages, we face potential competition from many different sources, including pharmaceutical and biotechnology companies, academic institutions and 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.

Our competitors may have significantly greater financial resources, established presence in the market, 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, sales, marketing 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.

There are currently no therapies approved to treat Galactosemia. Two companies have announced plans for preclinical or conceptual programs to develop gene therapies in Galactosemia. We believe these potential AAV gene therapies are several years away from entering the clinic, and there is no data to date in preclinical or clinical studies demonstrating efficacy or safety. Additionally, due to safety issues associated with AAV gene therapy in general, and the fact that Galactosemia is a debilitating but not life-threatening disease, we do not believe that the risk appetite of parents or physicians will support substantial competition from gene therapies.

There are currently no therapies approved for SORD Deficiency. There are no drugs in development to our knowledge outside of AT-007, and we believe that the IP licensed from University of Miami is sufficiently broad to encompass the entire class of aldose reductase inhibitors for treatment of SORD Deficiency.

There are currently no therapies approved to treat DbCM. Sponsors of sodium-glucose cotransporter-2, or SGLT2, inhibitors are pursuing broad cardiovascular labels in type 2 diabetes patients, which may include a subset of DbCM patients as part of the larger diabetic population at risk for heart failure. Many of these programs are sponsored by large pharmaceutical companies with a strong presence in cardiology and metabolic disease. There have been prior studies demonstrating effectiveness in DbCM of off-label use of sildenafil, although we do not believe this represents a commercially viable competitive threat.

There are no disease modifying therapies approved to treat DPN outside of Japan, India and China. In these limited markets, epalrestat, another ARI, is approved to prevent worsening of DPN, and despite challenges in compliance due to frequent dosing three to five times daily, the drugs are generic and offer a low cost alternative. A more effective therapy with improved tolerability and dosing may offer an advantage. A re-formulation of proprietary crystalline epalrestat, BNV-222, is in development for DPN in Russia in a 12-month Phase $^{2}/_{3}$ clinical trial, which completed enrollment in 2016, but has not yet reported any results.

There are several therapies approved to treat severe or late-stage forms of DR, or proliferative DR, such as diabetic macular edema and proliferative DR, including anti-VEGF therapies, Lucentis and Eylea, which represents approximately 20% of the larger DR population. There are currently no therapies approved to treat non-proliferative DR, an earlier stage of the disease upstream of vessel or capillary proliferation. However, there are significant additional clinical development efforts for other mechanistic interventions in early-stage or for non-proliferative DR.

Intellectual Property

Our intellectual property is critical to our business and we strive to protect it, including by obtaining and maintaining patent protection in the United States and internationally for our product candidates, new therapeutic approaches and potential indications, and other inventions that are important to our business. Our policy is to seek to protect our proprietary and intellectual property position by, among other methods, filing U.S. and foreign patent applications related to our proprietary technology, inventions and improvements that are important for the development and implementation of our business. We also rely on the skills, knowledge and experience of our scientific and technical personnel, as well as that of our advisors, consultants and other contractors. To help protect our proprietary know-how that is not patentable, we rely on confidentiality agreements to protect our interests. We require our employees, consultants and advisors to enter into confidentiality agreements prohibiting the disclosure of confidential information

and requiring disclosure and assignment to us of the ideas, developments, discoveries and inventions important to our business.

Our patent portfolio includes patents and patent applications that are exclusively licensed from Columbia University and patent applications that are owned by us. Our patent portfolio includes patents and patent applications that cover our product candidates AT-007, AT-001, and AT-003, and the use of these candidates for therapeutic purposes in certain territories. Our proprietary technology has been developed primarily through relationships with academic research centers and contract research organizations.

For our product candidates, we will, in general, initially pursue patent protection covering compositions of matter and methods of use. Throughout the development of our product candidates, we seek to identify additional means of obtaining patent protection that would potentially enhance commercial success, including through additional methods of use, process of making, formulation and dosing regimen-related claims.

In total, our patent portfolio, including patents licensed from Columbia University and patents owned by us, comprises nine different patent families, filed in various jurisdictions worldwide, including families directed to composition of matter for AR inhibitors, and families directed to methods of treating Galactosemia and complications associated with Galactosemia, SORD Deficiency and PMM2-CDG using AR inhibitors. Our patent portfolio includes issued patents in the United States, Europe, Japan, Australia, Canada, and other jurisdictions. Our patent portfolio is outlined below:

Composition of Matter Patents

AT-007. We have exclusively licensed a patent family from Columbia University that includes two issued composition of matter patents and two issued method use of patents in the United States, and 40 issued patents in Europe, Japan, Australia, India, Israel, China, Mexico and South Africa, that claim the composition of matter of and certain methods of use with respect to AT 007. In addition, we have pending patent applications in the United States, Europe, Japan, China, Canada, Australia, Russia, Brazil, India, Israel, Mexico, New Zealand, Singapore, South Africa, and Hong Kong. The 20-year term of patents in this family runs through June 2037, absent any available patent term adjustments or extensions.

AT-001 and AT-003. We have exclusively licensed from Columbia University a patent family that includes five issued patents in the United States, 82 issued patents in Europe, Japan, Canada, and Australia, a pending application in the United States and a pending application in Europe that claim the composition of matter of and certain methods of use with respect to AT-001 and AT-003. The 20-year term of the patents in this family runs through July 2031, absent any available patent term adjustments or extensions.

Methods for Treating Galactosemia

We own a family of patent applications that claims methods for treating Galactosemia and preventing complications associated with Galactosemia using AT-007 and other inhibitors of AR. This family currently includes granted patents in the United States and Mexico, and pending patent application in the United States, Europe, Japan, Australia, Brazil, Canada, China, Israel, Mexico, New Zealand, Russia, Singapore, South Africa, and Hong Kong. The 20-year term of patents in this family run through July 2038, absent any available patent term adjustments or extensions.

Methods for Treating SORD Deficiencies

We own a family of patent applications that claims methods for treating SORD Deficiency using AT-007 and other inhibitors of AR. This family currently includes pending patent applications in the United States, Europe, Japan, Australia, Brazil, Canada, China, Israel, Mexico, New Zealand, Russia, Singapore, South Africa and South Korea. No patents have issued to date, but we expect that the 20-year term of any patents that do issue in this family will run through 2041, absent any available patent term adjustments or extensions.

We have exclusively licensed a patent family from University of Miami that includes pending applications in the United States, Europe, Japan, Australia, Brazil, Canada, China, Israel, Mexico, New Zealand, India, Russia, Singapore, South Africa, South Korea and Hong Kong, that claims methods for treating inherited neuropathy using a variety of therapeutic modalities including inhibitors of AR. This patent family is owned by University of Miami, University of Rochester and UCL Business Ltd. and licensed to us by University of Miami pursuant to an exclusive agency granted to University of Miami, by University of Rochester and UCL Business Ltd. No patents have issued to date, but we expect that the 20-year term of any patents that do grant in this family will run through 2040, absent any available patent term adjustments or extensions.

Methods for Treating PMM2-CDG

We own a family of patent applications that claim methods for treating PMM2-CDG using AT-007 and other inhibitors of AR. This family currently includes pending patent application in the United States, Europe, Japan, Australia, Brazil, Canada, China, Israel, Mexico, New Zealand, Singapore, South Africa and Hong Kong. No patents have issued to date, but we expect that the 20-year term of any patents that do grant in this family will run through 2040, absent any available patent term adjustments or extensions.

We expect to file future patent applications on innovations that are developed in the course of advancing our pipeline through preclinical and clinical development.

Patent Term and Term Extensions

Individual patents have terms for varying periods depending on the date of filing of the patent application or the date of patent issuance and the legal term of patents in the countries in which they are obtained. Generally, utility patents issued for applications filed in the United States are granted a term of 20 years from the earliest effective filing date of a non-provisional patent application. In addition, in certain instances, the term of a U.S. patent can be extended to recapture a portion of the United States Patent and Trademark Office, or the USPTO, delay in issuing the patent as well as a portion of the term effectively lost as a result of the FDA regulatory review period. However, as to the FDA component, the restoration period cannot be longer than five years and the restoration period cannot extend the patent term beyond 14 years from FDA approval. In addition, only one patent applicable to an approved drug is eligible for the extension, and only those claims covering the approved drug, a method for using it, or a method of manufacturing may be extended. The duration of foreign patents varies in accordance with provisions of applicable local law, but typically is also 20 years from the earliest effective filing date. All taxes, annuities or maintenance fees for a patent, as required by the USPTO and various foreign jurisdictions, must be timely paid in order for the patent to remain in force during this period of time.

The actual protection afforded by a patent may vary on a product by product basis, from country to country, and can depend upon many factors, including the type of patent, the scope of its coverage, the availability of regulatory-related extensions and the availability of legal remedies in a particular country and the validity and enforceability of the patent.

Our patents and patent applications may be subject to procedural or legal challenges by others. We may be unable to obtain, maintain and protect the intellectual property rights necessary to conduct our business, and we may be subject to claims that we infringe or otherwise violate the intellectual property rights of others, which could materially harm our business. For more information, see the section titled “Risk Factors — Risks Related to Our Intellectual Property.”

Trademarks and Know-How

In connection with the ongoing development and advancement of our products and services in the United States and various international jurisdictions, we seek to create protection for our marks and enhance their value by pursuing trademarks and service marks where available and when appropriate. In addition to patent and trademark protection, we rely upon know-how and continuing technological innovation to develop and maintain our competitive position. We

seek to protect our proprietary information, in part, by using confidentiality agreements with our commercial partners, collaborators, employees and consultants, and invention assignment agreements with our employees and consultants. These agreements are designed to protect our proprietary information and, in the case of the invention assignment agreements, to grant us ownership of technologies that are developed by our employees and through relationships with third parties. These agreements may be breached, and we may not have adequate remedies for any breach. In addition, our trade secrets may otherwise become known or be independently discovered by competitors. To the extent that our contractors, commercial partners, collaborators, employees, and consultants use intellectual property owned by others in their work for us, disputes may arise as to the rights in related or resulting know-how and inventions. For more information, see the section titled "Risk Factors — Risks Related to Our Intellectual Property."

Government Regulation and Product Approval

Government authorities in the United States, at the federal, state and local levels, and in other countries, extensively regulate, among other things, the research, development, testing, manufacture, pricing, quality control, packaging, storage, recordkeeping, labeling, advertising, promotion, distribution, marketing, import and export of pharmaceutical products, such as those we are developing. The processes for obtaining regulatory approvals in the United States and in foreign countries, along with subsequent compliance with applicable statutes and regulations, require the expenditure of substantial time and financial resources.

United States Government Regulation

In the United States, the FDA regulates drugs under the Federal Food, Drug, and Cosmetic Act, or FDCA, and its implementing regulations. The process of obtaining regulatory approvals and the subsequent compliance with appropriate federal, state, local and foreign statutes and regulations requires the expenditure of substantial time and financial resources. Failure to comply with the applicable United States requirements at any time during the drug development process, approval process or after approval, may subject an applicant to delays and a variety of administrative or judicial sanctions, such as the FDA's refusal to approve a pending New Drug Application, or NDA, withdrawal of an approval, imposition of a clinical hold, issuance of warning or untitled letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, restitution, disgorgement or civil or criminal penalties.

The process required by the FDA before a drug may be marketed in the United States generally involves:

- completion of preclinical laboratory tests, animal studies and formulation studies in compliance with the FDA's good laboratory practice, or GLP, regulations;
- submission to the FDA of an IND, which must become effective before human clinical trials may begin;
- approval by an independent institutional review board, or IRB, at each clinical site before each trial may be initiated;
- performance of adequate and well-controlled clinical trials, in accordance with good clinical practice, or GCP, requirements to establish the safety and efficacy of the proposed drug for each indication;
- submission to the FDA of an NDA for marketing approval, which must include data from preclinical testing and clinical trials;
- satisfactory completion of an FDA advisory committee review, if applicable;
- satisfactory completion of an FDA pre-approval inspection of the manufacturing facility or facilities at which the product is produced to assess compliance with cGMP requirements, and to assure that the facilities, methods and controls are adequate to preserve the drug's identity, strength, quality and purity;

- satisfactory completion of an FDA inspection of selected clinical sites to assure compliance with GCPs and the integrity of the clinical data;

- payment of user fees; and

- FDA review and approval of the NDA.

Preclinical Studies

Preclinical studies include laboratory evaluation of product chemistry, toxicity and formulation, as well as animal studies to assess potential safety and efficacy. An IND sponsor must submit the results of the preclinical tests, together with manufacturing information, analytical data and any available clinical data or literature, among other things, to the FDA as part of an IND. Some preclinical testing may continue even after the IND is submitted. An IND automatically becomes effective 30 days after receipt by the FDA, unless before that time the FDA raises concerns or questions related to one or more proposed clinical trials and places the clinical trial on a clinical hold or a partial clinical hold.

In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. As a result, submission of an IND may not result in the FDA allowing clinical trials to commence.

Clinical Trials

Clinical trials involve the administration of the investigational new drug to human subjects under the supervision of qualified investigators in accordance with GCP requirements, which include the requirement that all research subjects provide their informed consent in writing for their participation in any clinical trial. Clinical trials are conducted under protocols detailing, among other things, the objectives of the trial, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated. A protocol for each clinical trial and any subsequent protocol amendments must be submitted to the FDA as part of the IND. In addition, an IRB at each institution participating in the clinical trial must review and approve the plan for any clinical trial before it commences at that institution, and the IRB must continue to oversee the clinical trial while it is being conducted and reapprove the study at least annually. Information about certain clinical trials must be submitted within specific timeframes to the National Institutes of Health, or NIH, for public dissemination on their ClinicalTrials.gov website. The Food and Drug Omnibus Reform Act, or FDORA, which was signed into law on December 29, 2022, made numerous amendments to the FDCA including provisions intended to, among other things, decentralize and modernize clinical trials and enhance diversity in clinical trial populations.

Human clinical trials are typically conducted in three sequential phases, which may overlap or be combined. In Phase 1, the drug is initially introduced into healthy human subjects or patients with the target disease or condition and tested for safety, dosage tolerance, absorption, metabolism, distribution, excretion and, if possible, to gain an initial indication of its effectiveness. In Phase 2, the drug typically is administered to a limited patient population to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the product for specific targeted diseases and to determine dosage tolerance and optimal dosage. In Phase 3, the drug is administered to an expanded patient population, generally at geographically dispersed clinical trial sites, in well-controlled clinical trials to generate enough data to statistically evaluate the safety and efficacy of the product for approval, to establish the overall risk-benefit profile of the product and to provide adequate information for the labeling of the product.

Progress reports detailing the results of the clinical trials must be submitted, at least annually, to the FDA, and more frequently if serious adverse events occur. Phase 1, Phase 2 and Phase 3 clinical trials may not be completed successfully within any specified period, or at all. Furthermore, the FDA or the sponsor may suspend or terminate a clinical trial at any time on various grounds, including a finding that the research subjects are being exposed to an unacceptable health risk. In addition, IND safety reports must be submitted to the FDA for any of the following: serious and unexpected suspected adverse reactions, findings from other studies or animal or in vitro testing that suggest a significant risk in humans exposed to the product, and any clinically important increase in the case of a serious suspected adverse reaction over that listed in the protocol or investigator brochure. Similarly, an IRB can suspend or terminate

approval of a clinical trial at its institution if the clinical trial is not being conducted in accordance with the IRB's requirements, or if the drug has been associated with unexpected serious harm to patients.

Marketing Approval

Assuming successful completion of the required clinical testing, the results of the preclinical and clinical studies, together with detailed information relating to the product's chemistry, manufacture, controls and proposed labeling, among other things, are submitted to the FDA as part of an NDA requesting approval to market the product for one or more indications. In most cases, the submission of an NDA is subject to a substantial application user fee. Under the Prescription Drug User Fee Act, or PDUFA, guidelines that are currently in effect, the FDA has a goal of ten months from the date of "filing" of a standard NDA for a new molecular entity to review and act on the submission. This review typically takes 12 months from the date the NDA is submitted to the FDA because the FDA has approximately two months to make a "filing" decision. The FDA may further extend the review process for three additional months to consider new information provided by the applicant to address any outstanding deficiency identified by the FDA following the original submission.

In addition, under the Pediatric Research Equity Act, certain NDAs or supplements to an NDA must contain data that are adequate 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 product is safe and effective. The FDA may, on its own initiative or at the request of the applicant, grant deferrals for submission of some or all pediatric data until after approval of the product for use in adults, or full or partial waivers from the pediatric data requirements. Unless otherwise required by regulation, the pediatric data requirements do not apply to products with orphan designation.

The FDA also may require submission of a risk evaluation and mitigation strategy, or REMS, plan to ensure that the benefits of the drug outweigh its risks. The REMS plan could include medication guides, physician communication plans, assessment plans, and/or elements to assure safe use, such as restricted distribution methods, patient registries or other risk minimization tools.

The FDA conducts a preliminary review of all NDAs within the first 60 days after submission, before accepting them for filing, to determine whether they are sufficiently complete to permit substantive review. The FDA may request additional information rather than accept an NDA for filing. In this event, the application must be resubmitted with the additional information. The resubmitted application is also subject to review before the FDA accepts it for filing. Once the submission is accepted for filing, the FDA begins an in-depth substantive review. The FDA reviews an NDA to determine, among other things, whether the drug is safe and effective and whether the facility in which it is manufactured, processed, packaged or held meets standards designed to assure the product's continued safety, quality and purity.

The FDA may refer an application for a novel drug to an advisory committee. An advisory committee is a panel of independent experts, including clinicians and other scientific experts, that reviews, evaluates and provides a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions.

Before approving an NDA, the FDA typically will inspect the facility or facilities where the product is manufactured. These pre-approval inspections may cover all facilities associated with an NDA submission, including component manufacturing, finished product manufacturing and control testing laboratories. The FDA will not approve an application 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. Additionally, before approving an NDA, the FDA will typically inspect one or more clinical trial sites to assure compliance with GCP requirements.

The testing and approval process for an NDA requires substantial time, effort and financial resources, and takes several years to complete. Data obtained from preclinical and clinical testing are not always conclusive and may be

susceptible to varying interpretations, which could delay, limit or prevent regulatory approval. The FDA may not grant approval of an NDA on a timely basis, or at all.

After evaluating the NDA and all related information, including the advisory committee recommendation, if any, and inspection reports regarding the manufacturing facilities and clinical trial sites, the FDA may issue an approval letter, or, in some cases, a complete response letter. A complete response letter generally contains a statement of specific conditions that must be met in order to secure final approval of the NDA and may require additional clinical or preclinical testing in order for FDA to reconsider the application. Even with submission of this additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval. If and when those conditions have been met to the FDA's satisfaction, the FDA will typically issue an approval letter. An approval letter authorizes commercial marketing of the drug with specific prescribing information for specific indications.

Even if the FDA approves a product, it may limit the approved indications for use of the product, require that contraindications, warnings or precautions be included in the product labeling, require that post-approval studies, including Phase 4 clinical trials, be conducted to further assess a drug's safety after approval, require testing and surveillance programs to monitor the product after commercialization, or impose other conditions, including distribution and use restrictions or other risk management mechanisms under a REMS, which can materially affect the potential market and profitability of the product. The FDA may prevent or limit further marketing of a product based on the results of post-marketing studies or surveillance programs. After approval, some types of changes to the approved product, such as adding new indications, manufacturing changes, and additional labeling claims, are subject to further testing requirements and FDA review and approval.

Orphan Drug Designation

Under the Orphan Drug Act, the FDA may grant orphan drug designation to a drug intended to treat a rare disease or condition, which is a disease or condition that affects fewer than 200,000 individuals in the United States, or if it affects more than 200,000, there is no reasonable expectation that sales of the drug in the United States will be sufficient to offset the costs of developing and making the drug available in the United States. Orphan drug designation must be requested before submitting an NDA. Orphan drug designation does not convey any advantage in or shorten the duration of the regulatory review and approval process.

If the FDA approves a sponsor's marketing application for a designated orphan drug for use in the rare disease or condition for which it was designated, the sponsor is eligible for a seven-year period of marketing exclusivity, during which the FDA may not approve another sponsor's marketing application for a drug with the same active moiety and intended for the same use or indication as the approved orphan drug, except in limited circumstances, such as if a subsequent sponsor demonstrates its product is clinically superior. During a sponsor's orphan drug exclusivity period, competitors, however, may receive approval for drugs with different active moieties for the same indication as the approved orphan drug, or for drugs with the same active moiety as the approved orphan drug, but for different indications. Orphan drug exclusivity could block the approval of one of our product candidates for seven years if a competitor obtains approval for a drug with the same active moiety intended for the same indication before we do, unless we are able to demonstrate that grounds for withdrawal of the orphan drug exclusivity exist, such as that our product is clinically superior. Further, if a designated orphan drug receives marketing approval for an indication broader than the rare disease or condition for which it received orphan drug designation, it may not be entitled to exclusivity.

Special FDA Expedited Review and Approval Programs

The FDA has various programs, including fast track designation, priority review, accelerated approval and breakthrough therapy designation, which are intended to expedite or simplify the process for the development and FDA review of drugs that are intended for the treatment of serious or life-threatening diseases or conditions and demonstrate the potential to address unmet medical needs. The purpose of these programs is to provide important new drugs to patients earlier than under standard FDA review procedures.

To be eligible for a fast track designation, the FDA must determine, based on the request of a sponsor, that a product is intended to treat a serious or life-threatening disease or condition and demonstrates the potential to address an

unmet medical need. The FDA will determine that a product will fill an unmet medical need if it will provide a therapy where none exists or provide a therapy that may be potentially superior to existing therapy based on efficacy or safety factors. The FDA may review sections of the NDA for a fast track product on a rolling basis before the complete application is submitted. The FDA may do so if the sponsor provides a schedule for the submission of the sections of the NDA, the FDA agrees to accept sections of the NDA and determines that the schedule is acceptable, and the sponsor pays any required user fees upon submission of the first section of the NDA.

The FDA may give a priority review designation to drugs that are designed to treat serious conditions, and if approved, would provide a significant improvement in treatment, or provide a treatment where no adequate therapy exists. A priority review means that the goal for the FDA to review an application is six months, rather than the standard review of ten months under current PDUFA guidelines. Under the current PDUFA agreement, these six and ten-month review periods are measured from the "filing" date rather than the receipt date for NDAs for new molecular entities, which typically adds approximately two months to the timeline for review and decision from the date of submission. Most products that are eligible for fast track designation are also likely to be considered appropriate to receive a priority review.

Rare pediatric disease, or RPD, designation by the FDA enables priority review voucher, or PRV, eligibility upon U.S. market approval of a designated drug for rare pediatric diseases. The RPD-PRV program is intended to encourage development of therapies to prevent and treat rare pediatric diseases. The voucher, which is awarded upon NDA or Biologics License Application, or BLA, approval to the sponsor of a designated RPD can be sold or transferred to another entity and used by the holder to receive priority review for a future NDA or BLA submission, which reduces the FDA review time of such future submission from ten to six months. The RPD-PRV program is currently scheduled to sunset as of September 30, 2026.

In addition, products studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit over existing treatments may be eligible for accelerated approval. To qualify, the FDA must determine that the drug product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, 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. As a condition of approval, the FDA may require a sponsor of a drug receiving accelerated approval to perform post-marketing studies to verify and describe the predicted effect on irreversible morbidity or mortality or other clinical endpoint, and the drug may be subject to accelerated withdrawal procedures. Among FDORA's provisions are amendments to the accelerated approval program, including new requirements relating to post-approval studies and enhanced enforcement and withdrawal authorities for the FDA.

Breakthrough therapy designation is for 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. The FDA must take certain actions, such as holding timely meetings and providing advice, intended to expedite the development and review of an application for approval of a breakthrough therapy.

Even if a product qualifies for one or more of these programs, the FDA may later decide that the product no longer meets the conditions for qualification or decide that the time period for FDA review or approval will not be shortened. We may explore some of these opportunities for our product candidates as appropriate.

Post-Approval Requirements

Drugs manufactured or distributed pursuant to FDA approvals are subject to pervasive and continuing regulation by the FDA, including, among other things, requirements relating to recordkeeping, periodic reporting, product sampling and distribution, advertising and promotion and reporting of adverse experiences with the product. After approval, most changes to the approved product, such as adding new indications, manufacturing changes or other labeling claims, are subject to further testing requirements and prior FDA review and approval. There also are continuing

annual user fee requirements for any marketed products and the establishments at which such products are manufactured, as well as application fees for supplemental applications with clinical data.

Even if the FDA approves a product, it may limit the approved indications for use of the product, require that contraindications, warnings or precautions be included in the product labeling, including a boxed warning, require that post-approval studies, including Phase 4 clinical trials, be conducted to further assess a drug's safety after approval, require testing and surveillance programs to monitor the product after commercialization, or impose other conditions, including distribution restrictions or other risk management mechanisms under a REMS, which can materially affect the potential market and profitability of the product. The FDA may prevent or limit further marketing of a product based on the results of post-marketing studies or surveillance programs.

In addition, drug manufacturers and other entities involved in the manufacture and distribution of approved drugs are required to register their establishments with the FDA and state agencies, and are subject to periodic unannounced inspections by the FDA and these state agencies for compliance with cGMP requirements.

Changes to the manufacturing process are strictly regulated and often require prior FDA approval before being implemented. FDA regulations also require investigation and correction of any deviations from cGMP and impose reporting and documentation requirements upon the sponsor and any third party manufacturers that the sponsor may decide to use. Accordingly, manufacturers must continue to expend time, money and effort in the area of production and quality control to maintain compliance with cGMP and other regulatory requirements.

The FDA may also subject a drug to official lot release, which requires manufacturers to submit several items to the FDA with respect to each lot of a drug before it is released to distribution. These items include samples of each lot, a summary of the manufacturing history of the lot and the results of any tests performed on the lot.

Once an approval is granted, the FDA may withdraw the approval if compliance with regulatory requirements and standards is not maintained or if problems occur after the product reaches the market.

Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, problems with manufacturing processes, or failure to comply with regulatory requirements, may result in mandatory revisions to the approved labeling to add new safety information; imposition of post-market studies or clinical trials to assess new safety risks; or imposition of distribution or other restrictions under a REMS program. Other potential consequences include, among other things:

- restrictions on the marketing or manufacturing of the product, complete withdrawal of the product from the market or product recalls;
- fines, warning letters or holds on post-approval clinical trials;
- refusal of the FDA to approve pending NDAs or supplements to approved NDAs, or suspension or revocation of product approvals;
- product seizure or detention, or refusal to permit the import or export of products; or
- injunctions or the imposition of civil or criminal penalties.

The FDA strictly regulates marketing, labeling, advertising and promotion of products that are placed on the market. Drugs may be promoted only for the approved indications and in accordance with the provisions of the approved label, although physicians, in the practice of medicine, may prescribe approved drugs for unapproved indications. The FDA and other agencies actively enforce the laws and regulations prohibiting their promotion of off-label uses, and a company that is found to have improperly promoted off-label uses may be subject to significant civil, criminal and administrative liability.

In addition, the distribution of prescription pharmaceutical products is subject to the Prescription Drug Marketing Act, or PDMA, which regulates the distribution of drugs and drug samples at the federal level, and sets minimum standards for the registration and regulation of drug distributors by the states. Both the PDMA and state laws limit the distribution of prescription pharmaceutical product samples and impose requirements to ensure accountability in distribution.

Federal and State Fraud and Abuse, Data Privacy and Security, and Transparency Laws and Regulations

In addition to FDA restrictions on marketing of pharmaceutical products, federal and state healthcare laws and regulations restrict business practices in the biopharmaceutical industry. These laws may impact, among other things, our current and future business operations, including our clinical research activities and proposed sales, marketing and education programs and constrain the business or financial arrangements and relationships with healthcare providers and other parties through which we may market, sell and distribute any products for which we obtain marketing approval. These laws include anti-kickback and false claims laws and regulations, data privacy and security, and transparency laws and regulations, including, without limitation, those laws described below.

The federal Anti-Kickback Statute prohibits any person or entity from, among other things, knowingly and willfully offering, paying, soliciting or receiving remuneration to induce or in return for purchasing, leasing, ordering or arranging for or recommending the purchase, lease or order of any item or service reimbursable under Medicare, Medicaid or other federal healthcare programs. The term "remuneration" has been broadly interpreted to include anything of value. The federal Anti-Kickback Statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on the one hand and prescribers, purchasers and formulary managers on the other. Although there are a number of statutory exceptions and regulatory safe harbors protecting some common activities from prosecution, the exceptions and safe harbors are drawn narrowly. Practices that involve remuneration that may be alleged to be intended to induce prescribing, purchases or recommendations may be subject to scrutiny if they do not qualify for an exception or safe harbor. Several courts have interpreted the statute's intent requirement to mean that if any one purpose of an arrangement involving remuneration is to induce referrals of federal healthcare covered business, the statute has been violated.

A person or entity does not need to have actual knowledge of this statute or specific intent to violate it in order to have committed a violation. In addition, the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the federal civil False Claims Act or the civil monetary penalties laws.

Federal civil and criminal false claims laws and civil monetary penalties laws, including the federal civil False Claims Act, which can be enforced by individuals through civil whistleblower or qui tam actions, prohibits any person or entity from, among other things, knowingly presenting, or causing to be presented, a false claim for payment to the federal government or knowingly making, using or causing to be made or used a false record or statement material to a false or fraudulent claim to the federal government. A claim includes "any request or demand" for money or property presented to the U.S. government. Several pharmaceutical and other healthcare companies have been prosecuted under these laws for allegedly providing free product to customers with the expectation that the customers would bill federal programs for the product. Other companies have been prosecuted for causing false claims to be submitted because of the companies' marketing of products for unapproved, and thus non-reimbursable, uses.

The federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, created additional federal criminal statutes that prohibit, among other things, knowingly and willfully executing a scheme to defraud any healthcare benefit program, including private third party payors and knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false, fictitious or fraudulent statement in connection with the delivery of or payment for healthcare benefits, items or services. Also, many states have similar fraud and abuse statutes or regulations that apply to items and services reimbursed under Medicaid and other state programs, or, in several states, apply regardless of the payor.

In addition, we may be subject to data privacy and security regulation by both the federal government and the states in which we conduct our business. HIPAA, as amended by the Health Information Technology for Economic and

Clinical Health Act, or HITECH, and their respective implementing regulations, impose specified requirements on certain types of individuals and entities relating to the privacy, security and transmission of individually identifiable health information. Among other things, HITECH makes HIPAA's security standards directly applicable to "business associates," defined as independent contractors or agents of covered entities, which include certain healthcare providers, healthcare clearinghouses and health plans, that create, receive, maintain or transmit individually identifiable health information in connection with providing a service for or on behalf of a covered entity. HITECH also 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 HIPAA and seek attorney's fees and costs associated with pursuing federal civil actions. In addition, state laws govern the privacy and security of health information in certain circumstances, many of which are not pre-empted by HIPAA, differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts.

The federal Physician Payments Sunshine Act requires certain manufacturers of drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program, with specific exceptions, to report annually to the Centers for Medicare & Medicaid Services, or CMS, information related to payments or other transfers of value made to physicians and teaching hospitals, and applicable manufacturers and applicable group purchasing organizations to report annually to CMS ownership and investment interests held by physicians and their immediate family members.

We may also be subject to state laws that require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government, state laws that require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures, and state and local laws that require the registration of pharmaceutical sales representatives. State legislatures are increasingly focused on pharmaceutical company activities, and we may be subject to additional new state or federal legislative requirements in the future that could impact our ability to commercialize our product candidates, if they are approved.

Because of the breadth of these laws and the narrowness of available statutory exceptions and regulatory safe harbors, it is possible that some of our business activities could be subject to challenge under one or more of such laws. If our operations are found to be in violation of any of the federal and state laws described above or any other governmental regulations that apply to us, we may be subject to significant criminal, civil and administrative penalties including damages, fines, individual imprisonment, additional reporting requirements and oversight if we become subject to a corporate integrity agreement or similar agreement to resolve allegations of non-compliance with these laws, contractual damages, reputational harm, diminished profits and future earnings, disgorgement, exclusion from participation in government healthcare programs 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. To the extent that any of our product candidates are sold in a foreign country, we may be subject to similar foreign laws and regulations, which may include, for instance, applicable post-marketing requirements, including safety surveillance, anti-fraud and abuse laws, implementation of corporate compliance programs, reporting of payments or transfers of value to healthcare professionals, and additional data privacy and security requirements.

Coverage and Reimbursement

The future commercial success of our product candidates, if approved, will depend in part on the extent to which third party payors, such as governmental payor programs at the federal and state levels, including Medicare and Medicaid, private health insurers and other third party payors, provide coverage of and establish adequate reimbursement levels for our product candidates. Third party payors generally decide which products they will pay for and establish reimbursement levels for those products. In particular, in the United States, no uniform policy for coverage and reimbursement exists. Private health insurers and other third party payors often provide coverage and reimbursement for products based on the level at which the government, through the Medicare program, provides coverage and reimbursement for such products, but also on their own methods and approval process apart from Medicare determinations. Therefore, coverage and reimbursement can differ significantly from payor to payor.

In the United States, the European Union, or EU, and other potentially significant markets for our product candidates, government authorities and third party payors are increasingly attempting to limit or regulate the price of products, particularly for new and innovative products, which often has resulted in average selling prices lower than they would otherwise be. Further, the increased emphasis on managed healthcare in the United States and on country and regional pricing and reimbursement controls in the EU will put additional pressure on product pricing, reimbursement and usage. These pressures can arise from rules and practices of managed care groups, judicial decisions and laws and regulations related to Medicare, Medicaid and healthcare reform, pharmaceutical coverage and reimbursement policies and pricing in general.

Third party payors are increasingly imposing additional requirements and restrictions on coverage and limiting reimbursement levels for products. For example, federal and state governments reimburse products at varying rates generally below average wholesale price. These restrictions and limitations influence the purchase of products. Third party payors may limit coverage to specific products on an approved list, or formulary, which might not include all of the FDA-approved products for a particular indication. Third party payors are increasingly challenging the price and examining the medical necessity and cost-effectiveness of products, in addition to their safety and efficacy. We may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost-effectiveness of our product candidates, in addition to the costs required to obtain the FDA approvals. Our product candidates may not be considered medically necessary or cost-effective. A payor's decision to provide coverage for a product does not imply that an adequate reimbursement rate will be approved. Adequate third party payor reimbursement may not be available to enable us to realize an appropriate return on our investment in product development. Legislative proposals to reform healthcare or reduce costs under government insurance programs may result in lower reimbursement for our product candidates, if approved, or exclusion of our product candidates from coverage and reimbursement. The cost containment measures that third party payors and providers are instituting and any healthcare reform could significantly reduce our revenues from the sale of any approved product candidates.

Healthcare Reform

The United States and some foreign jurisdictions are considering enacting or have enacted a number of additional legislative and regulatory proposals to change the healthcare system in ways that could affect our ability to sell our product candidates. The United States and some foreign jurisdictions are considering enacting or have enacted a number of additional legislative and regulatory proposals to change the healthcare system in ways that could affect our ability to sell our product candidates profitably, if approved. Among policy makers and payors in the United States and elsewhere, there is significant interest in promoting changes in healthcare systems with the stated goals of containing healthcare costs, improving quality and expanding access. In the United States, the pharmaceutical industry has been a particular focus of these efforts, which include major legislative initiatives to reduce the cost of care through changes in the healthcare system, including limits on the pricing, coverage, and reimbursement of pharmaceutical and biopharmaceutical products, especially under government-funded healthcare programs, and increased governmental control of drug pricing.

There have been several U.S. government initiatives over the past few years to fund and incentivize certain comparative effectiveness research, including creation of the Patient-Centered Outcomes Research Institute under the Patient Protection and Affordable Care Act of 2010, as amended by the Health Care and Education Reconciliation Act of 2010, or collectively the PPACA. It is also possible that comparative effectiveness research demonstrating benefits in a competitor's product could adversely affect the sales of our product candidates.

The PPACA became law in March 2010 and substantially changed the way healthcare is financed by third party payors, and significantly impacts the U.S. pharmaceutical industry. Among other measures that may have an impact on our business, the PPACA establishes an annual, nondeductible fee on any entity that manufactures or imports specified branded prescription drugs and biologic agents; a new Medicare Part D coverage gap discount program; and a new formula that increases the rebates a manufacturer must pay under the Medicaid Drug Rebate Program. Additionally, the PPACA extends manufacturers' Medicaid rebate liability, expands eligibility criteria for Medicaid programs, and expands entities eligible for discounts under the Public Health Service Act.

In addition to these provisions, the Affordable Care Act established a number of bodies whose work may have a future impact on the market for certain pharmaceutical products. These include the Patient-Centered Outcomes Research Institute, established to oversee, identify priorities in, and conduct comparative clinical effectiveness research and the Center for Medicare and Medicaid Innovation within the Centers for Medicare and Medicaid Services, to test innovative payment and service delivery models to lower Medicare and Medicaid spending. At this time, we are unsure of the full impact that the PPACA will have on our business.

Since its enactment, there have been judicial and Congressional challenges to certain aspects of the PPACA and we expect such challenges and amendments to continue. Former President Trump implemented certain directives designed to delay the implementation of certain PPACA provisions or otherwise circumvent requirements for health insurance mandated by the PPACA, while Congress has considered legislation that would repeal or repeal and replace all or part of the PPACA. While Congress has not passed comprehensive repeal legislation, bills affecting the implementation of the PPACA have been signed into law. For example, the Tax Act includes a provision that repealed, effective January 1, 2019, the tax-based shared responsibility payment imposed by the PPACA on certain individuals who fail to maintain qualifying health coverage for all or part of a year that is commonly referred to as the "individual mandate." On December 19, 2020, former President Trump signed a bill that repealed the PPACA's so-called "Cadillac" tax on certain high cost employer-sponsored insurance plans. The Bipartisan Budget Act of 2018, or the BBA, among other things, amended the PPACA, effective January 1, 2019, to increase from 50% to 70% the point-of-sale discount that is owed by pharmaceutical manufacturers who participate in Medicare Part D and to close the coverage gap in most Medicare drug plans, commonly referred to as the "donut hole." In December 2018, a U.S. District Court Judge in the Northern District of Texas, or Texas District Court Judge, ruled that the individual mandate is a critical and inseverable feature of the PPACA, and therefore, because it was repealed as part of the Tax Act, the remaining provisions of the PPACA are invalid as well. In December 2019, the U.S. Court of Appeals for the Fifth Circuit upheld the lower court decision, which was then appealed to the U.S. Supreme Court. In June 2021, the U.S. Supreme Court held that state and individual plaintiffs did not have standing to challenge the individual mandate provision of the PPACA; in so holding, the Supreme Court did not consider larger constitutional questions about the validity of this provision or the validity of the PPACA in its entirety. Another case challenging the PPACA's requirement that private insurers cover certain preventative services is currently pending before the same U.S. District Court Judge in the Northern District of Texas who ruled against the individual mandate in 2018. In September 2022, the judge held that certain preventative services violated the U.S. Constitution and set a schedule for additional briefing regarding the scope of the remedy. That briefing was completed in January 2023 and it is unclear when or how the court will rule. It is also unclear how this or any potential future litigation and other efforts to repeal and replace the PPACA will impact the PPACA, or our business.

Further, there has been increasing legislative, executive branch, and enforcement interest in the United States with respect to drug pricing practices. Specifically, there have been several recent U.S. Congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drugs. With respect to executive branch actions, the former Trump administration released a "Blueprint" to lower drug prices and reduce out of pocket costs of drugs that contained proposals to increase manufacturer competition, increase the negotiating power of certain federal healthcare programs, incentivize manufacturers to lower the list price of their products and reduce the out of pocket costs of drug products paid by consumers. The HHS has implemented some of these measures under its existing authority. For example, in May 2019, CMS issued a final rule to allow Medicare Advantage Plans the option of using step therapy for Part B drugs, beginning January 1, 2020. Although a number of these and other proposed measures will require authorization through additional legislation to become effective, Congress and the Biden administration have each indicated that it will continue to seek new legislative and/or administrative measures to control drug costs. For example, the Inflation Reduction Act of 2022, enacted on August 16, 2022, seeks to reduce prescription drug costs by, among other provisions, allowing Medicare to negotiate prices for certain high-cost prescription drugs in Medicare Parts B and D, imposing an excise tax on pharmaceutical manufacturers that refuse to negotiate pricing with Medicare, requiring inflation rebates to limit annual drug price increases in Medicare, redesigning the Medicare Part D formula, and limiting the cost-sharing for insulin products. It is unclear whether additional drug pricing and other healthcare reform measures will be enacted, and if enacted, what effect they would have on our business.

At the state level, legislatures 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. In addition, regional healthcare authorities and individual hospitals are increasingly using bidding procedures to determine which drugs and suppliers will be included in their healthcare programs. These measures could reduce future demand for our products or put pressure on our pricing.

Additionally, in May 2018, the Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew Bellina Right to Try Act of 2017, or the Right to Try Act, was signed into law. The law, among other things, provides a federal framework for certain patients to access certain investigational new drug products that have completed a Phase I clinical trial and that are undergoing investigation for FDA approval. Under certain circumstances, eligible patients can seek treatment without enrolling in clinical trials and without obtaining FDA permission under the FDA expanded access program. There is no obligation for a drug manufacturer to make its drug products available to eligible patients as a result of the Right to Try Act.

Foreign Regulation

In order to market any product outside of the United States, we would need to comply with numerous and varying regulatory requirements of other countries regarding safety and efficacy and governing, among other things, clinical trials, marketing authorization, commercial sales and distribution of our product candidates. For example, in the EU, we must obtain authorization of a clinical trial application, or CTA, in each member state in which we intend to conduct a clinical trial. Whether or not we obtain FDA approval for a drug, we would need to obtain the necessary approvals by the comparable regulatory authorities of foreign countries before we can commence clinical trials or marketing of the drug in those countries. The approval process varies from country to country and can involve additional product testing and additional administrative review periods. The time required to obtain approval in other countries might differ from and be longer than that required to obtain FDA approval. Regulatory approval in one country does not ensure regulatory approval in another, but a failure or delay in obtaining regulatory approval in one country may negatively impact the regulatory process in others.

Facilities

We are currently in a five-year lease for the space for our principal executive offices in New York, New York and a three-year lease for the offices in Englewood Cliffs, New Jersey. We believe that our facilities are adequate to meet our current needs.

Employees and Human Capital Resources

Investing in, developing, and maintaining human capital is critical to our success. As of December 31, 2022, we had 27 full-time employees, 18 of whom were primarily engaged in research and development activities. A total of ten employees have an M.D. or Ph.D. degree. We emphasize a number of measures and objectives in managing our human capital assets, including, among others, employee safety and wellness, talent acquisition and retention, employee engagement, development and training, diversity and inclusion and compensation and pay equity. None of our employees are represented by a labor union and we consider our employee relations to be good.

Our human capital resource objectives include, as applicable, identifying, recruiting, retaining, incentivizing and integrating our existing and new employees and advisors. The principal purposes of our equity and cash incentive plans are to attract, retain and reward personnel and increase our success and stockholder value thereby.

The success of our business is fundamentally connected to the well-being of our employees. Accordingly, we are committed to their health, safety and wellness.

Information About Our Executive Officers

The following table sets forth information regarding our executive officers:

Name	Age	Position(s)
Executive Officers		
Shoshana Shendelman, Ph.D.	44	President, Chief Executive Officer and Chair of the Board of Directors
Riccardo Perfetti, M.D., Ph.D.	63	Chief Medical Officer
Adam Hansard	47	Chief Commercial Officer

Shoshana Shendelman, Ph.D., age 44, is our founder and has served as our President and Chief Executive Officer and as chair of our board of directors since January 2016. Prior to founding our company, she founded Clearpoint Strategy Group LLC, a boutique life sciences consulting firm, where she served as the Managing Director from July 2012 to December 2016, and served as a Senior Advisor from January 2017 to December 2018. Prior to that, she served as a scientific consultant and analyst at Bridge Scientific Consulting LLC. Dr. Shendelman received her B.S. in biochemistry from Brandeis University and a Ph.D. in Cellular, Molecular and Biophysical Studies (CMBS) from Columbia University Vagelos College of Physicians and Surgeons. We believe that Dr. Shendelman's extensive knowledge of our company as founder, President and Chief Executive Officer and her management background and experience in the healthcare industry qualifies her to serve on our board of directors.

Riccardo Perfetti, M.D., Ph.D., age 63, has served as our Chief Medical Officer since August 2018. Prior to joining us, Dr. Perfetti served as a Senior Medical Officer, Vice President and Head of Global Medical Affairs, Diabetes and Cardiovascular Business Unit at Sanofi S.A., a publicly traded pharmaceutical company from October 2007 to September 2018. Prior to joining Sanofi, Dr. Perfetti served in various roles at Amgen Inc., a publicly traded biopharmaceutical company, including as a Director and Global Development Leader in diabetes, obesity, metabolism and endocrinology from December 2004 to August 2007. Dr. Perfetti was previously an associate professor of medicine at University of California in Los Angeles and a professor of medicine at the National Institutes of Health, or NIH. Dr. Perfetti practiced as an endocrinologist at Cedars-Sinai Medical Center and also served as Director of the Diabetes Research Laboratory and Director of the Outpatient Diabetes Program. Dr. Perfetti received his M.D. and Ph.D. in Endocrinology from University La Sapienza in Rome, Italy and received post-graduate training in endocrinology and molecular biology at NIH.

Adam Hansard, age 47, has served as our Chief Commercial Officer since March 2020. Prior to joining us, he was Senior Director of New Product Strategy at Alexion Pharmaceuticals, a biopharmaceutical company, from March 2019 to February 2020. From February 2018 to March 2019, he was Vice President of Business Operations at Syntimmune, a clinical-stage biotech purchased by Alexion in November 2018. From January 2012 to March 2018, Mr. Hansard worked at Sanofi Genzyme, a biotechnology company and wholly-owned subsidiary of Sanofi, a publicly traded, multinational pharmaceutical company, where he served as the North American Senior Director, Chief of Staff of MS Oncology and Immunology and the Senior Director of MS Brand Communications. Mr. Hansard received his Master's in Business Communication from Jones International University and his B.S. in Marketing from the University of West Florida.

Other Information

We were incorporated in Delaware in January 2016 and completed the IPO in May 2019. Our principal executive offices are located at 545 5th Avenue, Suite 1400, New York, New York 10017, and our telephone number is (212) 220-9226.

We maintain a website at www.appliedtherapeutics.com. The contents of our website are not incorporated in, or otherwise to be regarded as part of this Annual Report. Unless the context otherwise requires, the terms, “Applied Therapeutics,” the “Company,” “we,” “us,” “our” and the “ registrant” refer to Applied Therapeutics, Inc.

Investors and others should note that we announce material financial information to our investors using our investor relations website (http://ir.appliedtherapeutics.com), SEC filings, press releases, public conference calls and webcasts.

ITEM 1A. RISK FACTORS.

An investment in shares of our common stock involves a high degree of risk. You should carefully consider the following information about these risks described below, together with other information appearing elsewhere in this Annual Report, including our financial statements and the related notes and the section titled "Management's Discussion and Analysis of Financial Condition and Results of Operations," before deciding whether to invest in our common stock. The occurrence of any of the events or developments described below could harm our business, financial condition, results of operations and growth prospects. In such an event, the market price of our common stock could decline and you may lose all or part of your investment.

Additional risks and uncertainties not presently known to us or that we currently deem immaterial also may impair our business operations and the market price of our common stock.

Risk Factor Summary

The following is a summary of the risk factors included in this Item 1A and is qualified entirely by the disclosure included in the rest of this Item 1A:

Risks Related to Our Financial Position and Capital Needs

- We have incurred and expect to continue to incur substantial operating losses and our ability to use our net operating losses to offset future taxable income may be subject to certain limitations.
- Our operating history makes evaluating our business and future viability more difficult.
- We will require substantial additional funding to finance our operations, and may suffer consequences to our development programs upon failure to do so.
- Raising additional capital may cause adverse effects.

Risks Related to the Development and Commercialization of Our Product Candidates

- Our success is substantially dependent on the successful clinical development, regulatory approval and commercialization of our product candidates and may be adversely affected upon failure to do so.
- We or Advanz Pharma may fail to perform under any of the agreements entered into in connection with the partnership for the commercialization of AT-007, which may subject us to liabilities, and we may fail to achieve anticipated benefits of the partnership.
- Success in preclinical studies or earlier clinical trials may not be indicative of results in future clinical trials and our results may not be sufficient for the necessary regulatory approvals.
- Clinical drug development involves a lengthy and expensive process and the development of additional product candidates is risky and uncertain.
- We may be unable to obtain/maintain or receive the benefits of regulatory approval, rare pediatric disease designation/exclusivity, accelerated registration pathways, breakthrough therapy designations or fast track designations for our product candidates, as applicable.
- Clinical trials are expensive, time consuming and subject to factors outside our control.
- Our product candidates may cause undesirable side effects, affecting regulatory approval, commercial potential or result in significant negative consequences following any potential marketing approval.
- Interim, "top line" and preliminary data from our clinical trials may be subject to change.
- The market opportunities for our product candidates may be smaller than we believe or approval we obtain may narrow our patient population.
- We may face substantial competition.
- We may face risks related to strategic collaborations to develop our product candidates
- Our product candidates may fail to achieve market acceptance necessary for commercial success.
- We may face risks related to any potential international operations.
- We may be adversely affected by product liability lawsuits.
- Our insurance policies may be inadequate and potentially expose us to unrecoverable risks.

Risks Related to Regulatory Compliance

- We are subject to healthcare laws and regulations, which carry substantial penalties for noncompliance.
- Coverage and adequate reimbursement may not be available for our product candidates.
- Healthcare reform measures may have a negative impact on our business and results of operations.

Risks Related to Our Dependence on Third Parties

- Third-parties may conduct our preclinical studies and clinical trials in an unsatisfactory manner.
- We intend to rely on third parties to produce supplies of our product candidates.
- We and our third-party affiliates are subject to environmental, health and safety laws and regulations.

Risks Related to Our Intellectual Property

- Breaches of our license agreements may result in the adverse effects to our ability to continue the development and commercialization of our product candidates.
- Insufficient patent protection could allow our competitors to develop and commercialize products and technology similar or identical to ours.
- Obtaining and maintaining our patent rights is expensive, complicated and labor intensive and patent terms may be inadequate to protect our competitive position on our product candidates.
- We may be subject to claims alleging violations of intellectual property rights.
- Changes in patent law could impair our ability to protect our product candidates.
- We may be unable to protect our intellectual property rights.
- Intellectual property rights do not necessarily address all potential threats to our business.

Risks Related to Our Business Operations, Employee Matters and Managing Growth

- We are highly dependent on the services of our current executive officers.
- We may experience difficulties resulting from the expansion of our organization.
- We may be subject to security breaches in our information technology systems.
- Our employees and the third-parties we deal with may engage in misconduct or improper activities.
- Our business may be adversely affected by the coronavirus outbreak.

Risks Related to Ownership of Our Common Stock

- The market price of our common stock is volatile and has fluctuated substantially.
- Concentration of ownership of our common stock among our existing executive officers, directors and principal stockholders may prevent new investors from influencing significant corporate decisions.
- We do not anticipate paying any cash dividends on our capital stock in the foreseeable future.
- Failure to regain compliance with the continued listing requirements of Nasdaq could result in our common stock being delisted from Nasdaq and the price and liquidity of our common stock could be negatively impacted.

General Risk Factors

- We may be affected by unfavorable research or reports.
- We may use our cash and cash equivalents ineffectively or in ways with which you do not agree.
- We are subject to risks as an “emerging growth company” and a public company.
- We may avail ourselves of defensive and forum selection provisions in our governing documents and under Delaware law.

Risks Related to Our Financial Position and Capital Needs

We have incurred significant operating losses since inception and anticipate that we will continue to incur substantial operating losses for the foreseeable future and may never achieve or maintain profitability.

Since inception in January 2016, we have incurred significant operating losses. Our net loss was $82.5 million and $105.6 million for the years ended December 31, 2022 and 2021, respectively. As of December 31, 2022, we had an accumulated deficit of $348.8 million. We expect to continue to incur significant expenses and increasing operating losses for the foreseeable future. Since inception, we have devoted substantially all of our efforts to research and preclinical and clinical development of our product candidates, organizing and staffing our company, business planning, raising capital, establishing our intellectual property portfolio and conducting clinical trials. To date, we have never obtained regulatory approval for, or commercialized, any drugs. It could be several years, if ever, before we have a commercialized drug. The net losses we incur may fluctuate significantly from quarter to quarter and year-to-year. We anticipate that our expenses will increase substantially if, and as, we:

- continue the ongoing and planned development of our product candidates;
- initiate, conduct and complete any ongoing, anticipated or future preclinical studies and clinical trials for our current and future product candidates;
- seek marketing approvals for any product candidates that successfully complete clinical trials;
- establish a sales, marketing, manufacturing and distribution infrastructure to commercialize any current or future product candidate for which we may obtain marketing approval;
- seek to discover and develop additional product candidates;
- continue to build a portfolio of product candidates through the acquisition or in-license of drugs, product candidates or technologies;
- maintain, protect and expand our intellectual property portfolio;
- meet the requirements and demands of being a public company;
- defend against any product liability claims or other lawsuits related to our products;
- hire additional clinical, regulatory and scientific personnel; and
- add operational, financial and management information systems and personnel, including personnel to support our product development and planned future commercialization efforts.

Furthermore, we have incurred additional costs associated with operating as a public company, including significant legal, accounting, investor relations and other expenses.

To become and remain profitable, we must succeed in developing and eventually commercializing drugs that generate significant revenue. This will require us to be successful in a range of challenging activities, including completing preclinical studies and clinical trials of our current and future product candidates, obtaining regulatory approval, procuring commercial-scale manufacturing, marketing and selling any products for which we obtain regulatory approval (including through third parties), as well as discovering or acquiring and developing additional product candidates. We are only in the preliminary stages of most of these activities. We may never succeed in these activities and, even if we do, may never generate revenues that are sufficient to offset our expenses and achieve profitability.

Because of the numerous risks and uncertainties associated with drug development, we are unable to accurately predict the timing or amount of expenses or when, or if, we will be able to achieve profitability. If we are required by regulatory authorities to perform studies in addition to those currently expected, or if there are any delays in the initiation and completion of our clinical trials or the development of any of our product candidates, our expenses could increase.

Even if we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to become and remain profitable would decrease the value of our company and could impair our ability to raise capital, maintain our research and development efforts, expand our business or continue our operations. A decline in the value of our common stock could also cause you to lose all or part of your investment.

The report of our independent registered public accounting firm included a "going concern" explanatory paragraph.

The report of our independent registered public accounting firm on our financial statements for the year ended December 31, 2022 includes an explanatory paragraph regarding the existence of substantial doubt about our ability to continue as a going concern. Our cash and cash equivalents were $30.6 million at December 31, 2022. We also received a $10.7 million upfront payment from Advanz Pharma in January 2023 in conjunction with signing the exclusive licensing agreement for European commercialization rights. We believe that our cash and cash equivalents as of December 31, 2022, along with the upfront payment received in January 2023 and the projected clinical and regulatory milestone payments expected in fiscal year 2023 from Advanz Pharma will be sufficient to fund our operations through year end 2023, and potentially beyond if clinical trial completion and marketing authorization in Europe as well as commercial sales milestones materialize in the expected timelines. However, given our planned expenditures for the next several years, we have concluded, and our independent registered public accounting firm has agreed with our conclusion that there is still a substantial doubt regarding our ability to continue as a going concern for a period of 12 months beyond the filing of this Annual Report on Form 10-K. Any such inability to continue as a going concern may result in our stockholders losing their entire investment. There is no guarantee that we will become profitable or secure additional financing on acceptable terms.

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

We are a clinical-stage company with limited operational history, and our operations to date have been largely focused on raising capital, organizing and staffing our company, identifying and developing our product candidates, and undertaking preclinical and clinical development for our product candidates. As an organization, we have not yet demonstrated an ability to successfully complete clinical development, obtain regulatory approvals, manufacture a commercial-scale product or conduct sales and marketing activities necessary for successful commercialization, or arrange for a third party to conduct these activities on our behalf. Consequently, any predictions about our future success or viability may not be as accurate as they could be if we had a longer operating history.

We have encountered, and may continue to encounter unforeseen expenses, difficulties, complications, delays and other known or unknown factors in achieving our business objectives. We will need to transition at some point from a company with a research and development focus to a company capable of supporting commercial activities. We may not be successful in such a transition.

Additionally, we expect our financial condition and operating results to continue to fluctuate 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 will require substantial additional funding to finance our operations. If we are unable to raise capital when needed, we could be forced to delay, reduce or terminate certain of our development programs or other operations.

As of December 31, 2022, our cash, cash equivalents and marketable securities was $30.6 million. We also received a $10.7 million upfront payment from Advanz Pharma in January 2023 in conjunction with signing the exclusive licensing agreement for European commercialization rights. We believe that our cash and cash equivalents as of December 31, 2022, along with the upfront payment received in January 2023 and the projected clinical and regulatory milestone payments expected in fiscal year 2023 from Advanz Pharma will be sufficient to fund our operations through year end 2023, and potentially beyond if drug approvals materialize in the expected timelines. Based on our current operating and research and development plans, a substantial doubt exists regarding whether our existing cash, cash equivalents, and marketable securities will be sufficient to fund our projected operations through the next 12 months from the date the financial statements were issued. We will need to obtain substantial additional funding in connection with our continuing operations and planned research and clinical development activities. Our future capital requirements will depend on many factors, including:

- the timing, progress and results of our ongoing preclinical studies and clinical trials of our product candidates;
- the scope, progress, results and costs of preclinical development, laboratory testing and clinical trials of other product candidates that we may pursue;
- our ability to establish collaborations on favorable terms, if at all;
- the costs, timing and outcome of regulatory review of our product candidates;
- the costs and timing of future commercialization activities, including product manufacturing, marketing, sales and distribution, for any of our product candidates for which we receive marketing approval;
- the revenue, if any, received from commercial sales of our product candidates for which we receive marketing approval;
- the cost of any milestone and royalty payments with respect to any approved product candidates;
- the costs and timing of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending any intellectual property-related claims;
- the costs of operating as a public company; and
- the extent to which we acquire or in-license other product candidates and technologies.

Identifying potential product candidates and conducting preclinical testing and clinical trials is a time-consuming, expensive and uncertain process that takes years to complete, and we may never generate the necessary data or results required to obtain regulatory approval and achieve product sales. In addition, our product candidates, if approved, may not achieve commercial success. Our commercial revenues, if any, will be derived from sales of drugs that we do not expect to be commercially available for several years, if at all. Accordingly, we will need to continue to rely on additional financing to achieve our business objectives. 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.

In addition, our ability to access additional capital has been affected by overall macroeconomic trends, among other things, including rising interest rates, which have caused the price of our common stock to fluctuate significantly and/or decline. These macroeconomic trends have been exacerbated by recent hostilities between Russia and Ukraine, which have contributed to further economic instability in the global financial markets. As a result, adequate additional financing may not be available to us when needed or on attractive terms. If we are unable to raise capital when needed or on attractive terms, we could be forced to delay, reduce, or altogether terminate our research and development programs or future commercialization efforts.

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

Until such time, if ever, as we can generate substantial product revenue, we expect to finance our cash needs through public or private equity or debt financings, including through the Cowen Equity Distribution Agreement, third party funding, marketing and distribution arrangements, as well as other collaborations, strategic alliances and licensing arrangements, or any combination of these approaches. We do not have any committed external source of funds. To the extent that we raise additional capital through the sale of equity or convertible debt securities, your ownership interest in our company may be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect your rights as a stockholder. Debt and equity financings, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as redeeming our shares, making investments, incurring additional debt, making capital expenditures, declaring dividends or placing limitations on our ability to acquire, sell or license intellectual property rights.

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

Our ability to use our net operating losses to offset future taxable income may be subject to certain limitations.

We have incurred substantial losses since inception and do not expect to become profitable in the near future, if ever. In general, under Section 382 of the United States Internal Revenue Code of 1986, as amended, or the Code, a corporation that undergoes an "ownership change" is subject to limitations on its ability to utilize its pre-change NOLs to offset future taxable income. We may have experienced ownership changes in the past and may experience ownership changes in the future as a result of subsequent changes in our stock ownership (some of which shifts are outside our control). As a result, if, and to the extent that we earn net taxable income, our ability to use our pre-change NOLs to offset such taxable income may be subject to limitations.

For NOLs arising in tax years beginning after December 31, 2017, the Code limits a taxpayer's ability to utilize NOL carryforwards to 80% of taxable income. In addition, NOLs arising in tax years ending after December 31, 2017 can be carried forward indefinitely, but carryback is generally prohibited. NOLs generated in tax years beginning before January 1, 2018 will not be subject to the taxable income limitation, and NOLs generated in tax years ending before January 1, 2018 will continue to have a two-year carryback and 20-year carryforward period. Deferred tax assets for NOLs will need to be measured at the applicable tax rate in effect when the NOL is expected to be utilized. The limitations in the carryforward/carryback periods, as well as the limitation on use of NOLs for NOLs arising in tax years beginning after December 31, 2017 may significantly impact our ability to utilize our NOLs to offset taxable income in the future.

In order to realize the future tax benefits of our NOL carryforwards, we must generate taxable income, of which there is no assurance. Accordingly, we have provided a full valuation allowance for deferred tax assets as of December 31, 2021 and 2022.

Risks Related to the Development and Commercialization of Our Product Candidates

Our future success is substantially dependent on the successful clinical development, regulatory approval and commercialization of our product candidates. If we are not able to obtain required regulatory approvals, we will not be able to commercialize our product candidates and our ability to generate product revenue will be adversely affected.

We have invested a significant portion of our time and financial resources in the development of AT-007, AT-001 and AT-003. Our business is dependent on our ability to successfully complete development of, obtain regulatory approval for, and, if approved, successfully commercialize our product candidates in a timely manner. We may face unforeseen challenges in our drug development strategy, and we can provide no assurances that our drug design will prove to be effective, that we will be able to take advantage of expedited regulatory pathways for any of our product candidates, or that we will ultimately be successful in our future clinical trials.

We have not obtained regulatory approval for any product candidate, and it is possible that any product candidates we may seek to develop in the future will not obtain regulatory approval. Neither we nor any future collaborator is permitted to market any product candidates in the United States or abroad until we receive regulatory approval from the FDA or applicable foreign regulatory agency. The time required to obtain approval or other marketing authorizations by the FDA and comparable foreign regulatory authorities is unpredictable and typically takes many years following the commencement of clinical trials and depends upon numerous factors, including the substantial discretion of the regulatory authorities. In addition, approval policies, regulations or the type and amount of clinical data necessary to gain approval may change during the course of a product candidate's clinical development and may vary among jurisdictions.

Prior to obtaining approval to commercialize any product candidate in the United States or abroad, we must demonstrate with substantial evidence from well-controlled clinical trials, and to the satisfaction of the FDA or comparable foreign regulatory authorities, that such product candidate is safe and effective for its intended uses. Results from preclinical studies and clinical trials can be interpreted in different ways. Even if we believe that the preclinical or clinical data for our product candidates are promising, such data may not be sufficient to support approval by the FDA

and other regulatory authorities. The FDA may also require us to conduct additional preclinical studies or clinical trials for our product candidates either prior to or post-approval, or it may object to elements of our clinical development program, requiring their alteration.

Of the large number of products in development, only a small percentage successfully complete the FDA or comparable foreign regulatory authorities approval processes and are commercialized. The lengthy approval or marketing authorization process as well as the unpredictability of future clinical trial results may result in our failing to obtain regulatory approval or marketing authorization to market our product candidates, which would significantly harm our business, financial condition, results of operations and prospects.

Even if we eventually complete clinical testing and receive approval of a new drug application, or NDA, or foreign marketing for our product candidates, the FDA or the comparable foreign regulatory authorities may grant approval or other marketing authorization contingent on the performance of costly additional clinical trials, including post-market clinical trials. The FDA or the comparable foreign regulatory authorities also may approve or authorize for marketing a product candidate for a more limited indication or patient population than we originally request, and the FDA or comparable foreign regulatory authorities may not approve or authorize the labeling that we believe is necessary or desirable for the successful commercialization of a product candidate. Any delay in obtaining, or inability to obtain, applicable regulatory approval or other marketing authorization would delay or prevent commercialization of that product candidate and would adversely impact our business and prospects.

In addition, the FDA or comparable foreign regulatory authorities may change their policies, adopt additional regulations or revise existing regulations or take other actions, which may prevent or delay approval of our future product candidates under development on a timely basis. Such policy or regulatory changes could impose additional requirements upon us that could delay our ability to obtain approvals, increase the costs of compliance or restrict our ability to maintain any marketing authorizations we may have obtained.

Furthermore, even if we obtain regulatory approval for our product candidates, we will still need to develop a commercial organization, establish a commercially viable pricing structure and obtain approval for coverage and adequate reimbursement from third party and government payors, including government health administration authorities. If we are unable to successfully commercialize our product candidates, we may not be able to generate sufficient revenue to continue our business.

We or Advanz Pharma may fail to perform under any of the agreements entered into in connection with the partnership for commercialization of AT-007, which may subject us to liabilities, and we may fail to achieve anticipated benefits of the partnership.

In January 2023, we announced a partnership with Advanz Pharma ("Advanz") for commercialization of AT-007 (govorestat) in Europe, and entered into an Exclusive License and Supply Agreement (the "Advanz Agreement") with Advanz. Under the terms of the Advanz Agreement, Advanz receives exclusive commercial rights in the European Economic Area, Switzerland, and the UK (the "Territory") for AT-007 in Galactosemia and SORD Deficiency, with certain rights to future indications for AT-007 in the Territory. In return, we have the right to receive certain near-term development milestone payments upon clinical trial completion and marketing authorization in Europe as well as commercial sales milestones, which in the aggregate are expected to amount to over €130 million. We also have the right to receive royalties on any future net sales of AT-007 in the Territory of 20%. The royalty rate will be payable on a country-by-country basis until the later of (i) the expiration of the licensed patents covering the composition of matter of AT-007, or (ii) 10 years after the European Medicines Agency's grant of marketing authorization for AT-007. The royalties are subject to certain deductions, including certain secondary finishing costs, certain step-in establishment costs and a portion of fees for any potential third party patent licenses if applicable in the future. Following the initial term of the license, as described above, the royalty rate shall be reduced to 10% and shall continue in perpetuity unless the Advanz Agreement is terminated in various circumstances in accordance with its terms. We will continue to be responsible for the development, manufacturing and supply of AT-007, and Advanz will be responsible for packaging, distribution and commercialization in the Territory. The Advanz Agreement includes a sublicense under the 2016 Columbia Agreement and the 2020 Miami License Agreement.

Our partnership with Advanz is subject to various risks, including but not limited to the following:

- If Advanz breaches the contractual obligations owed to us pursuant to the Advanz Agreement or any related agreements, we could be exposed to commercial, regulatory or other liabilities.
- We may be subject to liabilities in connection with the development, manufacturing and supply of AT-007
- under the Advanz Agreement, including with respect to the 2016 Columbia Agreement and the 2020 Miami License Agreement.
- We may not be able to adequately protect our intellectual property or may become involved in intellectual property enforcement actions, which may cause us to incur substantial costs as a result of litigation or other proceedings relating to patent and other intellectual property rights, and such litigation may divert the attention of our management and scientific personnel and adversely affect our development and commercialization efforts.
- We may have limited control over the commercialization efforts of Advanz, and Advanz may fail to successfully sell and market AT-007.
- Our ability to receive certain economic benefits from the partnership, including the milestone payments and royalties, depends on certain contingencies beyond our control.
- In certain circumstances, Advanz may exercise certain step-in rights, including the ability for Advanz to perform its own supply arrangements, and in some cases, specified development rights in the Territory and assignment of certain contract rights. In all such circumstances, Advanz must continue to pay royalties and milestone payments, but may recoup certain of its manufacturing and development establishment costs, and deduct such costs from royalties owed.

Any of these factors could cause us to incur higher costs, disrupt the supply of our product candidates or approved products, delay the approval of our product candidates or prevent or disrupt the commercialization of our approved products. As a result, we may not achieve some or all economic benefits expected from the partnership.

The development of additional product candidates is risky and uncertain, and we can provide no assurances that we will be able to replicate our approach to drug development for other disease indications.

Efforts to identify, acquire or in-license, and then develop, product candidates require substantial technical, financial and human resources, whether or not any product candidates are ultimately identified. Our efforts may initially show promise in identifying potential product candidates, yet fail to yield product candidates for clinical development, approved products or commercial revenues for many reasons, including the following:

- the methodology used may not be successful in identifying potential product candidates;
- competitors may develop alternatives that render any product candidates we develop obsolete;
- any product candidates we develop may be covered by third parties' patents or other exclusive rights;
- a product candidate may be shown to have harmful side effects or other characteristics that indicate it is unlikely to be effective or otherwise does not meet applicable regulatory criteria;
- a product candidate may not be capable of being produced in commercial quantities at an acceptable cost, or at all; and
- a product candidate may not be accepted as safe and effective by physicians, patients, the medical community or third party payors.

We have limited financial and management resources and, 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 market potential. Our resource allocation decisions may cause us to fail to capitalize on viable commercial drugs or profitable market opportunities. 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 circumstances under which it would have been more advantageous for us to retain sole development and commercialization rights to such product candidate. In addition, we may not be successful in replicating our approach to drug development for other disease indications. If we are unsuccessful in identifying and developing additional product candidates or are unable to do so, our business may be harmed.

Success in preclinical studies or earlier clinical trials may not be indicative of results in future clinical trials and we cannot assure you that any ongoing, planned or future clinical trials will lead to results sufficient for the necessary regulatory approvals.

Success in preclinical testing and earlier clinical trials does not ensure that later clinical trials will generate the same results or otherwise provide adequate data to demonstrate the efficacy and safety of a product candidate. Preclinical studies and Phase 1 clinical trials are primarily designed to test safety, to study pharmacokinetics and pharmacodynamics and to understand the side effects of product candidates at various doses and schedules. Success in preclinical studies and earlier clinical trials does not ensure that later efficacy trials will be successful, nor does it predict final results. Our product candidates may fail to show the desired safety and efficacy in clinical development despite positive results in preclinical studies or having successfully advanced through earlier clinical trials.

In addition, the design of a clinical trial can determine whether its results will support approval of a product, and flaws in the design of a clinical trial may not become apparent until the clinical trial is well advanced. As an organization, we have limited experience designing clinical trials and may be unable to design and execute a clinical trial to support regulatory approval. Many companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in late-stage clinical trials even after achieving promising results in preclinical testing and earlier clinical trials. Data obtained from preclinical and clinical activities are subject to varying interpretations, which may delay, limit or prevent regulatory approval. In addition, we may experience regulatory delays or rejections as a result of many factors, including changes in regulatory policy during the period of our product candidate development. Any such delays could negatively impact our business, financial condition, results of operations and prospects.

Clinical drug development involves a lengthy and expensive process. We may incur additional costs and encounter substantial delays or difficulties in our clinical trials.

We may not commercialize, market, promote or sell any product candidate without obtaining marketing approval from the FDA or other comparable regulatory authority, and we may never receive such approvals. It is impossible to predict when or if any of our product candidates will prove effective or safe in humans and will receive regulatory approval. Before obtaining marketing approval from regulatory authorities for the sale of our product candidates, we must complete preclinical development and then conduct extensive clinical trials to demonstrate the safety and efficacy of our product candidates in humans. Clinical testing is expensive, is difficult to design and implement, can take many years to complete and is uncertain as to outcome.

A failure of one or more clinical trials can occur at any stage of testing. 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.

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

- delays in reaching a consensus with regulatory authorities on the design or implementation of our clinical trials;
- regulators or institutional review boards, or IRBs, may not authorize us or our investigators to commence a clinical trial or conduct a clinical trial at a prospective trial site;
- delays in reaching agreement on acceptable terms with prospective clinical research organizations, or CROs, and clinical trial sites;
- the number of patients required for clinical trials of our product candidates may be larger than we anticipate, enrollment in these clinical trials may be slower than we anticipate, participants may drop out of these clinical trials at a higher rate than we anticipate or fail to return for post-treatment follow-up or we may fail to recruit suitable patients to participate in a trial;
- clinical trials of our product candidates may produce negative or inconclusive results;

- imposition of a clinical hold by regulatory authorities as a result of a serious adverse event, concerns with a class of product candidates or after an inspection of our clinical trial operations, trial sites or manufacturing facilities;
- occurrence of serious adverse events associated with the product candidate that are viewed to outweigh its potential benefits;
- changes in regulatory requirements and guidance that require amending or submitting new clinical protocols; or
- we may decide, or regulators may require us, to conduct additional clinical trials or abandon product development programs.

Any inability to successfully complete preclinical and clinical development could result in additional costs to us or impair our ability to generate revenue from future drug sales or other sources. In addition, if we make manufacturing or formulation changes to our product candidates, we may need to conduct additional testing to bridge our modified product candidate to earlier versions. Clinical trial delays could also shorten any periods during which we may have the exclusive right to commercialize our product candidates, if approved, or allow our competitors to bring competing drugs to market before we do, which could impair our ability to successfully commercialize our product candidates and may harm our business, financial condition, results of operations and prospects.

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, or not obtain marketing approval at all;
- obtain approval for indications or patient populations that are not as broad as intended or desired;
- obtain approval with labeling that includes significant use or distribution restrictions or safety warnings, including in the form of a risk evaluation and mitigation strategy, or REMS;
- 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 REMS;
- be subject to the addition of labeling statements, such as warnings or contraindications;
- be sued; or
- experience damage to our reputation.

Our product development costs will also increase if we experience delays in testing or obtaining marketing approvals. 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 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 new drug applications, or INDs, or the conduct of these trials. Therefore, we cannot predict with any certainty the schedule for commencement and completion of future clinical trials. 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.

All of our current product candidates that have proceeded to clinical trials target inhibition of aldose reductase. There can be no assurance that aldose reductase inhibitors will ever receive regulatory approval.

All of our current product candidates that have proceeded to clinical trials target inhibition of the aldose reductase enzyme. There are no currently approved aldose reductase inhibitors on the market outside of Japan, India and China, and there can be no assurance that aldose reductase inhibitors will ever receive regulatory approval in all other

countries, including the United States. Prior attempts to inhibit this enzyme were hindered by nonselective, nonspecific inhibition, which resulted in limited efficacy and significant off-target safety effects. Our current product candidates, including AT-007, AT-001 and AT-003, may face similar or different challenges that prevent their successful commercialization.

We may not be able to obtain or maintain rare pediatric disease designation or exclusivity for our product candidates, which could limit the potential profitability of our product candidates.

We have obtained orphan drug designation and rare pediatric disease designation, from the FDA for AT-007 for the treatment of Galactosemia and PMM2-CDG. The FDA may grant orphan drug designation to a drug intended to treat a rare disease or condition, which is defined as a disease or condition that either affects fewer than 200,000 individuals in the United States, or if it affects more than 200,000 individuals, there is no reasonable expectation that sales of the drug in the United States will be sufficient to offset the costs of developing and making the drug available in the United States. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process.

For the purposes of the rare pediatric disease program, a "rare pediatric disease" is a serious or life-threatening disease in which the serious or life-threatening manifestations primarily affect individuals aged from birth to 18 years or a rare disease or conditions within the meaning of the Orphan Drug Act. Under the FDA's rare pediatric disease priority review voucher, or RPD-PRV, program, upon the approval of an NDA for the treatment of a rare pediatric disease, the sponsor of such application would be eligible for an RPD-PRV that can be used to obtain priority review for a subsequent NDA. The sponsor of the application may transfer (including by sale) the RPD-PRV 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. Congress has extended the RPD-PRV program until September 30, 2024, with potential for vouchers to be granted until 2026. This program has been subject to criticism, including by the FDA. As such it is possible that even though we have obtained qualification for a RPD-PRV, the program may no longer be in effect at the time of approval. Also, although priority review vouchers may be sold or transferred to third parties, there is no guaranty that we will be able to realize any value if we obtained, and subsequently were able to sell a priority review voucher. The RPD-PRV program is currently scheduled to sunset as of September 30, 2026.

A breakthrough therapy designation by the FDA for a product candidate may not lead to a faster development or regulatory review or approval process, and it would not increase the likelihood that the product candidate will receive marketing approval.

We may seek a breakthrough therapy designation for one or more product candidates. A breakthrough therapy is defined as a product candidate 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 product candidate may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. For product candidates 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. Product candidates 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.

Designation as a breakthrough therapy is within the discretion of the FDA. Accordingly, even if we believe that one of our product candidates meets the criteria for designation as a breakthrough therapy, the FDA may disagree and instead determine not to make such designation. In any event, the receipt of a breakthrough therapy designation for a product candidate may not result in a faster development process, review or approval compared to product candidates considered for approval under conventional FDA procedures and it would not assure ultimate approval by the FDA. In addition, even if one or more of our product candidates qualify as breakthrough therapies, the FDA may later decide that the product candidate no longer meets the conditions for qualification or it may decide that the time period for FDA review or approval will not be shortened.

We have sought, and may in the future seek, fast track designation from the FDA for our product candidates. Even if granted, fast track designation may not actually lead to a faster development, regulatory review or approval process.

If a product candidate is intended for the treatment of a serious or life-threatening condition and demonstrates the potential to address unmet needs for this condition, the sponsor may apply for FDA fast track designation. If fast track designation is obtained, the FDA may prioritize interactions with the sponsor concerning the designated development program and initiate review of sections of an NDA before the application is complete, known as "rolling review." Fast track designation would not ensure that we would experience a faster development, regulatory review or approval process compared to conventional FDA procedures or that we would ultimately obtain regulatory approval. Additionally, the FDA may withdraw fast track designation if it believes that the designation is no longer supported by data from our clinical development program.

We intend to seek approval from the FDA through the use of accelerated registration pathways. If we are unable to obtain approval under an accelerated pathway, we may be required to conduct additional preclinical studies or clinical trials, which could increase the expense of obtaining, reduce the likelihood of obtaining and/or delay the timing of obtaining, necessary marketing approvals. Even if we receive approval from the FDA to utilize an accelerated registration pathway, if our confirmatory trials do not verify clinical benefit, or if we do not comply with rigorous post-marketing requirements, the FDA may seek to withdraw accelerated approval.

We intend to seek an accelerated approval development pathway for our product candidates. Under the accelerated approval provisions of the Federal Food, Drug, and Cosmetic Act, or the FDCA, and the FDA's implementing regulations, the FDA may grant accelerated approval to a product designed to treat a serious or life-threatening condition that provides meaningful therapeutic advantage over available therapies and demonstrates an effect on a surrogate endpoint or intermediate clinical endpoint that is reasonably likely to predict clinical benefit. The FDA considers a clinical benefit to be a positive therapeutic effect that is clinically meaningful in the context of a given disease. For the purposes of accelerated approval, a surrogate endpoint is a marker, such as a laboratory measurement, radiographic image, physical sign or other measure that is thought to predict clinical benefit, but is not itself a measure of clinical benefit. An intermediate clinical endpoint is a clinical endpoint that can be measured earlier than an effect on irreversible morbidity or mortality that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit. The accelerated approval development pathway may be used in cases in which the advantage of a new drug over available therapy may not be a direct therapeutic advantage, but is a clinically important improvement from a patient and public health perspective. If granted, accelerated approval is contingent on the sponsor's agreement to conduct, in a diligent manner, additional post-approval confirmatory studies to verify and describe the drug's clinical profile or risks and benefits for accelerated approval. The FDA may require that any such confirmatory studies be initiated or substantially underway prior to the submission of an application for accelerated approval. If such post-approval studies fail to confirm the drug's clinical profile or risks and benefits, the FDA may withdraw its approval of the drug. FDORA made amendments to the accelerated approval program, among them new requirements relating to post-approval studies and enhanced enforcement and withdrawal authorities for the FDA, including in the event that a sponsor fails to comply with applicable requirements under the program. Because we are still in early stages of our clinical trials, we can provide no assurances that our biomarker-based approach will be successful in demonstrating a causal link to the relevant outcomes we are evaluating. If our approach is not successful, we may be required to conduct longer clinical trials.

If we choose to pursue accelerated approval, we intend to seek feedback from the FDA or will otherwise evaluate our ability to seek and receive such accelerated approval. There can be no assurance that, after our evaluation of the feedback from the FDA or other factors, we will decide to pursue or submit an NDA for accelerated approval or any other form of expedited development, review or approval. Furthermore, even if we submit an application for accelerated approval, there can be no assurance that the application will be accepted or that approval will be granted on a timely basis, or at all. The FDA also could require us to conduct further studies or trials prior to considering our application or granting approval of any type. We might not be able to fulfill the FDA's requirements in a timely manner, which would cause delays, or approval might not be granted because our submission is deemed incomplete by the FDA. A failure to obtain accelerated approval or any other form of expedited development, review or approval for a product candidate would result in a longer time period to commercialize such product candidate, could increase the cost of development of such product candidate and could harm our competitive position in the marketplace.

Even if we receive accelerated approval from the FDA, we will be subject to rigorous post-marketing requirements, including the completion of confirmatory post-market clinical trial(s) to verify the clinical benefit of the product, and submission to the FDA of all promotional materials prior to their dissemination. The FDA could seek to withdraw accelerated approval for multiple reasons, including if we fail to conduct any required post-market study with due diligence, a post-market study does not confirm the predicted clinical benefit, other evidence shows that the product is not safe or effective under the conditions of use, or we disseminate promotional materials that are found by the FDA to be false or misleading.

A failure to obtain accelerated approval or any other form of expedited development, review or approval for a product candidate that we may choose to develop would result in a longer time period prior to commercializing such product candidate, could increase the cost of development of such product candidate and could harm our competitive position in the marketplace.

Enrollment and retention of patients in clinical trials is an expensive and time-consuming process and could be delayed, made more difficult or rendered impossible by multiple factors outside our control.

Identifying and qualifying patients to participate in our clinical trials is critical to our success. We may encounter difficulties in enrolling patients in our clinical trials, thereby delaying or preventing development and approval of our product candidates. Even once enrolled, we may be unable to retain a sufficient number of patients to complete any of our trials. Patient enrollment and retention in clinical trials depends on many factors, including the size of the patient population, the nature of the trial protocol, the existing body of safety and efficacy data, the number and nature of competing treatments and ongoing clinical trials of competing therapies for the same indication, the proximity of patients to clinical sites and the eligibility criteria for the trial. Because our focus includes rare disorders, there are limited patient pools from which to draw in order to complete our clinical trials in a timely and cost-effective manner. Accordingly, enrollment of our clinical trials could take significantly longer than projected, which would delay any potential approval of our product candidates. Furthermore, even if we are able to enroll a sufficient number of patients for our clinical trials, we may have difficulty maintaining enrollment of such patients in our clinical trials.

Our efforts to build relationships with patient communities may not succeed, which could result in delays in patient enrollment in our clinical trials. Any negative results we may report in clinical trials of our product candidates may make it difficult or impossible to recruit and retain patients in other clinical trials of that same product candidate. Delays or failures in planned patient enrollment or retention may result in increased costs, program delays or both, which could have a harmful effect on our ability to develop our product candidates or could render further development impossible. In addition, we may rely on CROs and clinical trial sites to ensure proper and timely conduct of our future clinical trials and, while we intend to enter into agreements governing their services, we will be limited in our ability to ensure their actual performance.

For additional information regarding delays in enrollment and retention of patients, see "Risks Related to Our Business Operations, Employee Matters and Managing Growth—*Our business may be adversely affected by the coronavirus outbreak*."

Our product candidates may cause undesirable side effects or have other properties that could delay or prevent their regulatory approval, limit their commercial potential or result in significant negative consequences following any potential marketing approval.

During the conduct of clinical trials, patients report changes in their health, including illnesses, injuries and discomforts, to their doctor. Often, it is not possible to determine whether or not the product candidate being studied caused these conditions. Regulatory authorities may draw different conclusions or require additional testing to confirm these determinations, if they occur.

In addition, it is possible that as we test our product candidates in larger, longer and more extensive clinical trials, or as use of these product candidates becomes more widespread if they receive 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 subjects or patients. Many times, side effects are only

detectable after investigational drugs are tested in large-scale pivotal trials or, in some cases, after they are made available to patients on a commercial scale after approval. If additional clinical experience indicates that any of our product candidates have side effects or cause serious or life-threatening side effects, the development of the product candidate may fail or be delayed, or, if the product candidate has received regulatory approval, such approval may be revoked, which would harm our business, prospects, operating results and financial condition.

Interim, "top-line" and preliminary 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 publish interim, "top-line" or preliminary data from our clinical trials. Interim data from clinical trials that we may complete are subject to the risk that one or more of the clinical outcomes may materially change as patient enrollment continues and more patient data become available. Preliminary or "top-line" data also remain subject to audit and verification procedures that may result in the final data being materially different from the preliminary data we previously published. As a result, interim and preliminary data should be viewed with caution until the final data are available. Differences between preliminary or interim data and final data could significantly harm our business prospects and may cause the trading price of our common stock to fluctuate significantly.

The incidence and prevalence for target patient populations of our product candidates have not been established with precision. If the market opportunities for our product candidates are smaller than we believe they are or any approval we obtain is based on a narrower definition of the patient population, our business may suffer.

We currently focus our drug development on product candidates for the treatment of diseases with high unmet medical need. Our eligible patient population and pricing estimates may differ significantly from the actual market addressable by our product candidates. Our estimates of both the number of people who have these diseases, as well as the subset of people with these diseases who have the potential to benefit from treatment with our product candidates, are based on our beliefs and analyses. These estimates have been derived from a variety of sources, including the scientific literature, patient foundations or market research, and may prove to be incorrect. Further, new studies may change the estimated incidence or prevalence of the diseases we are targeting. The number of patients may turn out to be lower than expected. Likewise, the potentially addressable patient population for each of our product candidates may be limited or may not be receptive to treatment with our product candidates, and new patients may become increasingly difficult to identify or access. If the market opportunities for our product candidates are smaller than we estimate, we may not be able to achieve our forecast revenue, which could hinder our business plan and adversely affect our business and results of operations.

We may face substantial competition, which may result in others developing or commercializing drugs before or more successfully than us.

The development and commercialization of new drugs is highly competitive. We may face potential competition with respect to our current product candidates and may face competition with respect to any other product candidates that we may seek to develop or commercialize in the future from pharmaceutical and biotechnology companies, academic institutions, government agencies and other public and private research institutions.

Our competitors may have an advantage over us due to their greater size, resources and institutional experience. In particular, these companies have greater experience and expertise in securing reimbursement, government contracts and relationships with key opinion leaders, conducting testing and clinical trials, obtaining and maintaining regulatory approvals and distribution relationships to market products and marketing approved drugs. These companies also have significantly greater research and marketing capabilities than we do. If we are not able to compete effectively against existing and potential competitors, our business and financial condition may be harmed.

As a result of these factors, our competitors may obtain regulatory approval of their drugs before we are able to, which may limit our ability to develop or commercialize our product candidates. Our competitors may also develop therapies that are safer, more effective, more widely accepted or less expensive than ours, and may also be more successful than we are in manufacturing and marketing their drugs. These advantages could render our product

candidates obsolete or non-competitive before we can recover the costs of such product candidates' development and commercialization.

Mergers and acquisitions in the pharmaceutical and biotechnology industries may result in even more resources being concentrated among a smaller number of our competitors. Smaller and early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These third-parties compete with us in recruiting and retaining qualified scientific, management and commercial personnel, establishing clinical trial sites and subject registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs.

We may explore strategic collaborations that may never materialize or we may be required to relinquish important rights to and control over the development and commercialization of our product candidates to any future collaborators.

Over time, our business strategy includes acquiring or in-licensing additional product candidates for treatments of diseases with high unmet medical need. As a result, we intend to periodically explore a variety of possible strategic collaborations in an effort to gain access to additional product candidates or resources. These strategic collaborations may include partnerships with large strategic partners, particularly for the development of DPN treatments using AT-001. At the current time however, we cannot predict what form such a strategic collaboration might take. We are likely to face significant competition in seeking appropriate strategic collaborators, and strategic collaborations can be complicated and time consuming to negotiate and document. We may not be able to negotiate strategic collaborations on acceptable terms, or at all. We are unable to predict when, if ever, we will enter into any strategic collaborations because of the numerous risks and uncertainties associated with establishing them.

Future collaborations could subject us to a number of risks, including:

- we may be required to undertake the expenditure of substantial operational, financial and management resources;
- we may be required to issue equity securities that would dilute our stockholders' percentage ownership of our company;
- we may be required to assume substantial actual or contingent liabilities;
- we may not be able to control the amount and timing of resources that our strategic collaborators devote to the development or commercialization of our product candidates;
- strategic collaborators may select indications or design clinical trials in a way that may be less successful than if we were doing so;
- strategic collaborators may delay clinical trials, provide insufficient funding, terminate a clinical trial or abandon a product candidate, repeat or conduct new clinical trials or require a new version of a product candidate for clinical testing;
- strategic collaborators may not pursue further development and commercialization of products resulting from the strategic collaboration arrangement or may elect to discontinue research and development programs;
- strategic collaborators may not commit adequate resources to the marketing and distribution of our product candidates, limiting our potential revenues from these products;
- disputes may arise between us and our strategic collaborators that result in the delay or termination of the research, development or commercialization of our product candidates or that result in costly litigation or arbitration that diverts management's attention and consumes resources;
- strategic collaborators may experience financial difficulties;
- strategic collaborators may not properly maintain, enforce or defend our intellectual property rights or may use our proprietary information in a manner that could jeopardize or invalidate our proprietary information or expose us to potential litigation;
- business combinations or significant changes in a strategic collaborator's business strategy may adversely affect a strategic collaborator's willingness or ability to complete its obligations under any arrangement;

- strategic collaborators could decide to move forward with a competing product candidate developed either independently or in collaboration with others, including our competitors; and
- strategic collaborators could terminate the arrangement or allow it to expire, which would delay the development and may increase the cost of developing our product candidates.

Even if any product candidates receive marketing approval, they may fail to achieve market acceptance by physicians, patients, third party payors or others in the medical community necessary for commercial success.

Even if any product candidates receive marketing approval, they may fail to gain market acceptance by physicians, patients, third party payors and others in the medical community. If such product candidates do not achieve an adequate level of acceptance, we may not generate significant drug revenue and may not become profitable. The degree of market acceptance of any product candidate, if approved for commercial sale, will depend on a number of factors, including but not limited to:

- the convenience and ease of administration compared to alternative treatments and therapies;
- the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies;
- the efficacy and potential advantages compared to alternative treatments and therapies;
- the effectiveness of sales and marketing efforts;
- the strength of our relationships with patient communities;
- the cost of treatment in relation to alternative treatments and therapies, including any similar generic treatments;
- our ability to offer such drug for sale at competitive prices;
- the strength of marketing and distribution support;
- the availability of third party coverage and adequate reimbursement;
- the prevalence and severity of any side effects; and
- any restrictions on the use of the drug together with other medications.

Our efforts to educate physicians, patients, third-party payors and others in the medical community on the benefits of our product candidates may require significant resources and may never be successful. Such efforts may require more resources than are typically required due to the complexity and uniqueness of our product candidates. Because we expect sales of our product candidates, if approved, to generate substantially all of our revenues for the foreseeable future, the failure of our product candidates to find market acceptance would harm our business.

Even if we obtain regulatory approvals for our product candidates, they will remain subject to ongoing regulatory oversight.

Even if we obtain regulatory approvals for our product candidates, such approvals will be subject to ongoing regulatory requirements for manufacturing, labeling, packaging, storage, advertising, promotion, sampling, record keeping and submission of safety and other post-market information. Any regulatory approvals that we receive for our product candidates may also be subject to a REMS, limitations on the approved indicated uses for which the drug may be marketed or to the conditions of approval, or contain requirements for potentially costly post-marketing testing, including Phase 4 trials, and surveillance to monitor the quality, safety and efficacy of the drug. Such regulatory requirements may differ from country to country depending on where we have received regulatory approval.

In addition, drug manufacturers and their facilities are subject to payment of user fees and continual review and periodic inspections by the FDA and other regulatory authorities for compliance with current good manufacturing practices, or cGMP, requirements and adherence to commitments made in the NDA or foreign marketing application. If we, or a regulatory authority, discover previously unknown problems with a drug, such as adverse events of unanticipated severity or frequency, or problems with the facility where the drug is manufactured or if a regulatory authority disagrees with the promotion, marketing or labeling of that drug, a regulatory authority may impose restrictions relative to that drug, the manufacturing facility or us, including requesting a recall or requiring withdrawal of the drug from the market or suspension of manufacturing.

If we fail to comply with applicable regulatory requirements following approval of our product candidates, a regulatory authority may, among other actions:

- issue an untitled letter or warning letter asserting that we are in violation of the law;
- seek an injunction or impose administrative, civil or criminal penalties or monetary fines;
- suspend or withdraw regulatory approval;
- suspend any ongoing clinical trials;
- refuse to approve a pending NDA or comparable foreign marketing application or any supplements thereto submitted by us or our partners;
- restrict the marketing or manufacturing of the drug;
- seize or detain the drug or otherwise require the withdrawal of the drug from the market;
- refuse to permit the import or export of product candidates; or
- refuse to allow us to enter into supply contracts, including government contracts.

Moreover, the FDA strictly regulates the promotional claims that may be made about drug products. In particular, a product may not be promoted for uses that are not approved by the FDA as reflected in the product's approved labeling. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses, and a company that is found to have improperly promoted off-label uses may be subject to significant civil, criminal and administrative penalties.

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

The FDA's and other regulatory authorities' policies may change and additional laws or government regulations may be enacted that could prevent, limit or delay regulatory approval of our product candidates. If we are not able to maintain regulatory compliance with the FDCA, Cures Act, or other applicable requirements, we may lose any marketing approval that we may have obtained and we may not achieve or sustain profitability, which would adversely affect our business, prospects, financial condition and results of operations.

In addition, we cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative or executive action, either in the United States or abroad. For example, certain policies of the U.S. administration may impact our business and industry. It is difficult to predict how executive actions, including executive orders, may be implemented and the extent to which they will affect the FDA's ability to exercise its regulatory authority. If executive actions impose constraints on the FDA's ability to engage in oversight and implementation activities in the normal course, our business may be negatively impacted.

If we are unable to establish sales and marketing capabilities or enter into agreements with third parties to market and sell our product candidates, we may not be successful in commercializing them, if and when they are approved.

To successfully commercialize any product candidate that may result from our development programs, we will need to build out our sales and marketing capabilities, either on our own or with others. The establishment and development of our own commercial team or the establishment of a contract sales force to market any product candidate we may develop will be expensive and time-consuming and could delay any drug launch. Moreover, we cannot be certain that we will be able to successfully develop this capability. We may seek to enter into collaborations with other entities to utilize their established marketing and distribution capabilities, but we may be unable to enter into such agreements on favorable terms, if at all. If any current or future collaborators do not commit sufficient resources to commercialize our product candidates, or we are unable to develop the necessary capabilities on our own, we may be unable to generate sufficient revenue to sustain our business. We compete with many companies that currently have extensive, experienced and well-funded marketing and sales operations to recruit, hire, train and retain marketing and sales personnel. We will likely also face competition if we seek third parties to assist us with the sales and marketing

efforts of our product candidates. Without an internal team or the support of a third party to perform marketing and sales functions, we may be unable to compete successfully against these more established companies.

Even if we obtain and maintain approval for our product candidates from the FDA, we may never obtain approval outside the United States, which would limit our market opportunities.

Approval of a product candidate in the United States by the FDA does not ensure approval of such product candidate by regulatory authorities in other countries or jurisdictions, and approval by one foreign regulatory authority does not ensure approval by regulatory authorities in other foreign countries or by the FDA. Sales of our product candidates outside the United States will be subject to foreign regulatory requirements governing clinical trials and marketing approval. Even if the FDA grants marketing approval for a product candidate, comparable foreign regulatory authorities also must approve the manufacturing and marketing of the product candidate in those countries. Approval procedures vary among jurisdictions and can involve requirements and administrative review periods different from, and more onerous than, those in the United States, including additional preclinical studies or clinical trials. In many countries outside the United States, a product candidate must be approved for reimbursement before it can be approved for sale in that country. In some cases, the price that we intend to charge for any product candidates, if approved, is also subject to approval. Obtaining approval for our product candidates in the European Union from the European Commission following the opinion of the European Medicines Agency, or the EMA, if we choose to submit a marketing authorization application there, would be a lengthy and expensive process. Even if a product candidate is approved, the EMA may limit the indications for which the drug may be marketed, require extensive warnings on the drug labeling or require expensive and time-consuming additional clinical trials or reporting as conditions of approval. Obtaining foreign regulatory approvals and compliance with foreign regulatory requirements could result in significant delays, difficulties and costs for us and could delay or prevent the introduction of our product candidates in certain countries.

Further, clinical trials conducted in one country may not be accepted by regulatory authorities in other countries. Also, regulatory approval for our product candidates may be withdrawn. If we fail to comply with the applicable regulatory requirements, our target market will be reduced and our ability to realize the full market potential of our product candidates will be harmed and our business, financial condition, results of operations and prospects could be harmed.

If we commercialize our product candidates outside the United States, a variety of risks associated with international operations could harm our business.

We intend to seek approval to market our product candidates outside the United States, and may do so for future product candidates. If we market approved products outside the United States, we expect that we will be subject to additional risks in commercialization, including:

- different regulatory requirements for approval of therapies in foreign countries;
- reduced protection for intellectual property rights;
- unexpected changes in tariffs, trade barriers and regulatory requirements;
- economic weakness, including inflation, or political instability in particular foreign economies and markets;
- compliance with tax, employment, immigration and labor laws for employees living or traveling abroad;
- foreign currency fluctuations, which could result in increased operating expenses and reduced revenues, and other obligations incident to doing business in another country;
- foreign reimbursement, pricing and insurance regimes;
- workforce uncertainty in countries where labor unrest is more common than in the United States;
- production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad; and
- business interruptions resulting from geopolitical actions, including war and terrorism, international hostilities, or natural disasters including earthquakes, typhoons, floods and fires.

We have no prior experience in these areas. In addition, there are complex regulatory, tax, labor and other legal requirements imposed by many of the individual countries in which we may operate, with which we will need to comply. Many biopharmaceutical companies have found the process of marketing their products in foreign countries to be challenging.

Product liability lawsuits against us could cause us to incur substantial liabilities and could limit commercialization of any product candidate that we may develop.

We face an inherent risk of product liability exposure related to the testing of our product candidates in clinical trials and may face an even greater risk if we commercialize any product candidate that we may develop. If we cannot successfully defend ourselves against claims that any such product candidates caused injuries, we could incur substantial liabilities. Regardless of merit or eventual outcome, liability claims may result in:

- decreased demand for any product candidate that we may develop;
- loss of revenue;
- substantial monetary awards to trial participants or patients;
- significant time and costs to defend the related litigation;
- withdrawal of clinical trial participants;
- increased insurance costs;
- the inability to commercialize any product candidate that we may develop; and
- injury to our reputation and significant negative media attention.

Any such outcomes could negatively impact our business, financial condition, results of operations and prospects.

Our insurance policies may be inadequate and potentially expose us to unrecoverable risks.

Although we maintain product liability insurance coverage, such insurance may not be adequate to cover all liabilities that we may incur. We anticipate that we will need to increase our insurance coverage each time we commence a clinical trial and if we successfully commercialize any product candidate. Insurance availability, coverage terms and pricing continue to vary with market conditions. We endeavor to obtain appropriate insurance coverage for insurable risks that we identify; however, we may fail to correctly anticipate or quantify insurable risks, we may not be able to obtain appropriate insurance coverage and insurers may not respond as we intend to cover insurable events that may occur. We have observed rapidly changing conditions in the insurance markets relating to nearly all areas of traditional corporate insurance. Such conditions have resulted in higher premium costs, higher policy deductibles, and lower coverage limits. For some risks, we may not have or maintain insurance coverage because of cost or availability.

Risks Related to Regulatory Compliance

Our relationships with customers, physicians, and third party payors are subject, directly or indirectly, to federal and state healthcare fraud and abuse laws, false claims laws, health information privacy and security laws, and other healthcare laws and regulations. If we are unable to comply, or have not fully complied, with such laws, we could face substantial penalties.

Healthcare providers, physicians and third-party payors in the United States and elsewhere 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 professionals, principal investigators, consultants, customers and third-party payors subject us to various federal and state fraud and abuse laws and other healthcare laws, including, without limitation, the federal Anti-Kickback Statute, the federal civil and criminal false claims laws and the law commonly referred to as the Physician Payments Sunshine Act and regulations.

Ensuring that our business arrangements with third-parties comply with applicable healthcare laws and regulations will likely be costly. 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 participating in government-funded healthcare programs, such as Medicare and Medicaid, additional reporting requirements and oversight if we become subject to a corporate integrity agreement or similar agreement to resolve allegations of noncompliance with these laws, contractual damages, reputational harm and the curtailment or restructuring of our operations.

If the physicians or other providers or entities with whom we expect to do business are found not to be in compliance with applicable laws, they may be subject to criminal, civil or administrative sanctions, including exclusions from government-funded healthcare programs. Even if resolved in our favor, litigation or other legal proceedings relating to healthcare laws and regulations may cause us to incur significant expenses and could distract our technical and management personnel from their normal responsibilities. In addition, there could be public announcements of the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, it could have a substantial adverse effect on the price of our common shares. Such litigation or proceedings could substantially increase our operating losses and reduce the resources available for development, manufacturing, sales, marketing or distribution activities. Uncertainties resulting from the initiation and continuation of litigation or other proceedings relating to applicable healthcare laws and regulations could have an adverse effect on our ability to compete in the marketplace.

Coverage and adequate reimbursement may not be available for our product candidates, which could make it difficult for us to sell profitably, if approved.

Market acceptance and sales of any product candidates that we commercialize, if approved, will depend in part on the extent to which reimbursement for these drugs and related treatments will be available from third-party payors, including government health administration authorities, managed care organizations and other private health insurers. Third-party payors decide which therapies they will pay for and establish reimbursement levels. While no uniform policy for coverage and reimbursement exists in the United States, third-party payors often rely upon Medicare coverage policy and payment limitations in setting their own coverage and reimbursement policies. However, decisions regarding the extent of coverage and amount of reimbursement to be provided for any product candidates that we develop will be made on a payor-by-payor basis. Therefore, one payor's determination to provide coverage for a drug does not assure that other payors will also provide coverage, and adequate reimbursement, for the drug. Additionally, a third-party payor's decision to provide coverage for a therapy does not imply that an adequate reimbursement rate will be approved. Each payor determines whether or not it will provide coverage for a therapy, what amount it will pay the manufacturer for the therapy, and on what tier of its formulary it will be placed. The position on a payor's list of covered drugs, or formulary, generally determines the co-payment that a patient will need to make to obtain the therapy and can strongly influence the adoption of such therapy by patients and physicians. Patients who are prescribed treatments for their conditions and providers prescribing such services generally rely on third-party payors to reimburse all or part of the associated healthcare costs. Patients are unlikely to use our product candidates, if approved, unless coverage is provided and reimbursement is adequate to cover a significant portion of the cost of our products.

Third-party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular medications. We cannot be sure that coverage and reimbursement will be available for any drug that we commercialize and, if reimbursement is available, what the level of reimbursement will be. Inadequate coverage and reimbursement may impact the demand for, or the price of, any drug for which we obtain marketing approval. If coverage and adequate reimbursement are not available, or are available only at limited levels, we may not be able to successfully commercialize any product candidates that we develop.

Healthcare reform measures may have a negative impact on our business and results of operations.

In the United States and some foreign jurisdictions, there have been, and continue to be, several legislative and regulatory changes and proposed changes, as well as judicial challenges, regarding the healthcare system that could prevent or delay marketing approval of product candidates, restrict or regulate post-approval activities, and affect our ability to profitably sell any product candidates for which we obtain marketing approval. In particular, there have been

and continue to be a number of initiatives at the U.S. federal and state levels that seek to reduce healthcare costs and improve the quality of healthcare. For example, the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, or the MMA, changed the way Medicare covers and pays for pharmaceutical products. The legislation expanded Medicare coverage for drug purchases by the elderly and introduced a new reimbursement methodology based on average sales prices for physician-administered drugs. In addition, this legislation provided authority for limiting the number of drugs that will be covered in any therapeutic class. Cost reduction initiatives and other provisions of this legislation could decrease the coverage and price that we receive for any approved products. While the MMA applies only to drug benefits for Medicare beneficiaries, private payors often follow Medicare coverage policy and payment limitations in setting their own reimbursement rates. Therefore, any reduction in reimbursement that results from the MMA may result in a similar reduction in payments from private payors.

Further, in March 2010, the Patient Protection and Affordable Care Act of 2010, as amended by the Health Care and Education Reconciliation Act of 2010, or, collectively, the PPACA, was passed, which substantially changed the way healthcare is financed by both governmental and private payors in the United States. Some of the provisions of the PPACA have yet to be fully implemented, while certain provisions have been subject to executive, judicial and Congressional challenges. For example, the Tax Cuts and Jobs Act of 2017, or Tax Act includes a provision that repealed, effective January 1, 2019, the tax-based shared responsibility payment imposed by the PPACA on certain individuals who fail to maintain qualifying health coverage for all or part of a year, which is commonly referred to as the "individual mandate." Additionally, on January 22, 2018, then-President Trump signed a continuing resolution on appropriations for fiscal year 2018 that delayed the implementation of certain PPACA-mandated fees, including the so-called "Cadillac" tax on certain high-cost employer-sponsored insurance plans, the annual fee imposed on certain health insurance providers based on market share, and the medical device excise tax on non-exempt medical devices. Further, the Bipartisan Budget Act of 2018, or the BBA, among other things, amended the PPACA, effective January 1, 2019, to close the coverage gap in most Medicare drug plans, commonly referred to as the "donut hole." In July 2018, CMS published a final rule permitting further collections and payments to and from certain PPACA-qualified health plans and health insurance issuers under the PPACA adjustment program in response to the outcome of federal district court litigation regarding the method CMS uses to determine this risk adjustment. On December 14, 2018, a U.S. District Court Judge in the Northern District of Texas, or Texas District Court Judge, ruled that the individual mandate was a critical and inseverable feature of the PPACA, and therefore, because it was repealed as part of the Tax Act, the remaining provisions of the PPACA were invalid as well. In December 2019, the U.S. Court of Appeals for the Fifth Circuit upheld the lower court decision, which was then appealed to the U.S. Supreme Court. The U.S. Supreme Court heard arguments in the case in November 2020 and issued its decision in June 2021, ruling that the plaintiffs lacked the standing to challenge the individual mandate provision. In so holding, the Supreme Court did not consider larger constitutional questions about the validity of this provision or the validity of the PPACA in its entirety. Another case challenging the PPACA's requirement that insurers cover certain preventative services is currently pending before the same U.S. District Court Judge in the Northern District of Texas who ruled against the individual mandate in 2018. In September 2022, the judge held that certain preventative services violated the U.S. Constitution and set a schedule for additional briefing that will expand into January 2023. It is unclear how this or any potential future litigation and other efforts to repeal and replace the PPACA will impact the PPACA. Congress may consider additional legislation to repeal or repeal and replace other elements of the PPACA. We continue to evaluate the effect that the PPACA and its possible repeal and replacement may have on our business and the potential profitability of our product candidates.

Other legislative changes have been proposed and adopted since the PPACA was enacted. These changes include aggregate reductions to Medicare payments to providers of 2% per fiscal year pursuant to the Budget Control Act of 2011, which began in 2013, and due to subsequent legislative amendments to the statute, including the BBA, which will remain in effect through 2027 unless additional Congressional action is taken. The American Taxpayer Relief Act of 2012, among other things, further reduced Medicare payments to several providers, including hospitals and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years.

Additional changes that may affect our business include the expansion of programs such as Medicare payment for performance initiatives for physicians under the Medicare Access and CHIP Reauthorization Act of 2015. At this time, the full impact of the introduction of the Medicare quality payment program on overall physician reimbursement is unclear.

Further, in the United States there has been heightened governmental scrutiny over the manner in which 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 drug pricing, reduce the cost of prescription drugs under government payor programs, and review the relationship between pricing and manufacturer patient programs. While some of the proposed measures will require authorization through additional legislation to become effective, the U.S. Congress have indicated that they will continue to seek new legislative and/or administrative measures to control drug costs. For example, the Inflation Reduction Act of 2022 also seeks to reduce prescription drug costs by, among other provisions, allowing Medicare to negotiate prices for certain high-cost prescription drugs in Medicare Parts B and D, imposing an excise tax on pharmaceutical manufacturers that refuse to negotiate pricing with Medicare, requiring inflation rebates to limit annual drug price increases in Medicare, redesigning the Medicare Part D formula, and limiting cost-sharing for insulin products. It is unclear whether additional drug pricing and other healthcare reform measures will be enacted, and if enacted, what effect they would have on our business. We expect that additional U.S. federal healthcare reform measures will be adopted in the future, any of which could limit the amounts that the U.S. federal government will pay for healthcare products and services, which could result in reduced demand for our current or any future product candidates or additional pricing pressures. We cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative action in the United States or any other jurisdiction. If we or any third parties we may engage are slow or unable to adapt to changes in existing or new requirements or policies, or if we or such third parties are not able to maintain regulatory compliance, our current or any future product candidates we may develop may lose any regulatory approval that may have been obtained and we may not achieve or sustain profitability.

Further, on May 30, 2018, the Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew Bellina Right to Try Act of 2017, or the Right to Try Act, was signed into law. The law, among other things, provides a federal framework for certain patients to access certain investigational new drug products that have completed a Phase 1 clinical trial and that are undergoing investigation for FDA approval. Under certain circumstances, eligible patients can seek treatment without enrolling in clinical trials and without obtaining FDA permission under the FDA expanded access program. There is no obligation for a pharmaceutical manufacturer to make its drug products available to eligible patients as a result of the Right to Try Act.

We expect that these and other healthcare 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 drug, which could have an adverse effect on demand for our product candidates if they are approved. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private payors. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability or commercialize our product candidates.

Risks Related to Our Dependence on Third Parties

We intend to rely on third parties to produce clinical and commercial supplies of our product candidates.

We do not own or operate facilities for drug manufacturing, storage and distribution, or testing. We are dependent on third parties to manufacture the clinical supplies of our current and any future product candidates. The facilities used by our contract manufacturers to manufacture our product candidates must be approved by the FDA pursuant to inspections that will be conducted after we submit our NDA to the FDA. We do not control the manufacturing process of, and are completely dependent on, our contract manufacturing partners for compliance with the cGMP requirements, for manufacture of both active drug substance and finished drug product. If our contract manufacturers cannot successfully manufacture material that conforms to our specifications and the strict regulatory requirements of the FDA or others, we will not be able to secure and/or maintain regulatory approval for our product candidates. In addition, we have no control over the ability of our contract manufacturers to maintain adequate quality control, quality assurance and qualified personnel. If the FDA or a comparable foreign regulatory authority does not approve these facilities for the manufacture of our product candidates or if it withdraws any such approval in the future, we may need to find alternative manufacturing facilities, which would significantly impact our ability to develop, obtain regulatory approval for or market our product candidates, if approved. Any significant delay in the supply of a product candidate, or the raw material components thereof, for an ongoing clinical trial due to the need to replace a third-party

manufacturer could considerably delay completion of our clinical trials, product testing and potential regulatory approval of our product candidates.

We also intend to rely on third-party manufacturers to supply us with sufficient quantities of our product candidates to be used, if approved, for commercialization. We do not yet have a commercial supply agreement for commercial quantities of drug substance or drug product. If we are not able to meet market demand for any approved product, it would negatively impact our ability to generate revenue, harm our reputation, and could have an adverse effect on our business and financial condition.

Further, our reliance on third-party manufacturers entails risks to which we would not be subject if we manufactured product candidates ourselves, including:

- inability to meet our product specifications and quality requirements consistently;
- delay or inability to procure or expand sufficient manufacturing capacity;
- issues related to scale-up of manufacturing;
- costs and validation of new equipment and facilities required for scale-up;
- our third party manufacturers may not be able to execute our manufacturing procedures and other logistical support requirements appropriately;
- our third party manufacturers may fail to comply with cGMP requirements and other inspections by the FDA or other comparable regulatory authorities;
- our inability to negotiate manufacturing agreements with third parties under commercially reasonable terms, if at all;
- breach, termination or nonrenewal of manufacturing agreements with third parties in a manner or at a time that is costly or damaging to us;
- reliance on single sources for drug components;
- lack of qualified backup suppliers for those components that are currently purchased from a sole or single-source supplier;
- our third party manufacturers may not devote sufficient resources to our product candidates;
- we may not own, or may have to share, the intellectual property rights to any improvements made by our third party manufacturers in the manufacturing process for our product candidates;
- 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; and
- carrier disruptions or increased costs that are beyond our control.

In addition, if we enter into a strategic collaboration with a third party for the commercialization of our current or any future product candidates, we will not be able to control the amount of time or resources that they devote to such efforts. If any strategic collaborator does not commit adequate resources to the marketing and distribution of our product candidates, it could limit our potential revenues.

Any of these events could lead to clinical trial delays or failure to obtain regulatory approval, or impact our ability to successfully commercialize our current or any future product candidates once approved. Some of these events could be the basis for FDA action, including injunction, request for recall, seizure, or total or partial suspension of production.

Our business involves the use of hazardous materials and we and our third-party manufacturers and suppliers must comply with environmental, health and safety laws and regulations, which can be expensive and restrict how we do, or interrupt our, business.

Our research and development activities and our third-party manufacturers' and suppliers' activities involve the generation, storage, use and disposal of hazardous materials, including the components of our product candidates and other hazardous compounds and wastes. We and our manufacturers and suppliers are subject to environmental, health and safety laws and regulations governing, among other matters, the use, manufacture, generation, storage, handling, transportation, discharge and disposal of these hazardous materials and wastes and worker health and safety. In some

cases, these hazardous materials and various wastes resulting from their use are stored at our and our manufacturers' facilities pending their use and disposal. We cannot eliminate the risk of contamination or injury, which could result in an interruption of our commercialization efforts, research and development efforts and business operations, damages and significant cleanup costs and liabilities under applicable environmental, health and safety laws and regulations. We also cannot guarantee that the safety procedures utilized by our third-party manufacturers for handling and disposing of these materials and wastes generally comply with the standards prescribed by these laws and regulations. We may be held liable for any resulting damages, costs or liabilities, which could exceed our resources, and state or federal or other applicable authorities may curtail our use of certain materials and/or interrupt our business operations. Furthermore, environmental, health and safety laws and regulations are complex, change frequently and have tended to become more stringent. We cannot predict the impact of such changes and cannot be certain of our future compliance. Failure to comply with these environmental, health and safety laws and regulations may result in substantial fines, penalties or other sanctions. We do not currently carry environmental insurance coverage.

We rely on third-parties to conduct, supervise and monitor our preclinical studies and clinical trials, and if those third parties perform in an unsatisfactory manner, it may harm our business.

We do not currently have the ability to independently conduct any clinical trials. We intend to rely on CROs and clinical trial sites to ensure the proper and timely conduct of our preclinical studies and clinical trials, and we expect to have limited influence over their actual performance. We rely upon CROs to monitor and manage data for our clinical programs, as well as the execution of future preclinical studies. We expect to control only certain aspects of our CROs' activities. Nevertheless, we will be responsible for ensuring that each of our preclinical studies and clinical trials is conducted in accordance with the applicable protocol, legal, regulatory and scientific standards, and our reliance on the CROs does not relieve us of our regulatory responsibilities.

We and our CROs are required to comply with the good laboratory practices, or GLPs, and GCPs, which are regulations and guidelines enforced by the FDA and comparable foreign regulatory authorities in the form of International Conference on Harmonization guidelines for any of our product candidates that are in preclinical and clinical development. The regulatory authorities enforce GCPs through periodic inspections of trial sponsors, principal investigators and clinical trial sites. Although we rely on CROs to conduct GCP-compliant clinical trials, we remain responsible for ensuring that each of our GLP preclinical studies and clinical trials is conducted in accordance with its investigational plan and protocol and applicable laws and regulations. If we or our CROs fail to comply with GCPs, the clinical data generated in our clinical trials may be deemed unreliable, and the FDA or comparable foreign regulatory authorities may require us to perform additional clinical trials before approving our marketing applications. Accordingly, if our CROs fail to comply with these regulations or fail to recruit a sufficient number of subjects, we may be required to repeat clinical trials, which would delay the regulatory approval process.

Our reliance on third parties to conduct clinical trials will result in less direct control over the management of data developed through clinical trials than would be the case if we were relying entirely upon our own staff. Communicating with CROs and other third parties can be challenging, potentially leading to mistakes as well as difficulties in coordinating activities. Such parties may:

- have staffing difficulties;
- fail to comply with contractual obligations;
- experience regulatory compliance issues; or
- undergo changes in priorities or become financially distressed.

These factors may adversely affect the willingness or ability of third parties to conduct our clinical trials and may subject us to unexpected cost increases that are beyond our control. If our CROs do not successfully carry out their contractual duties or obligations, fail to meet expected deadlines, or fail to comply with regulatory requirements, or if the quality or accuracy of the clinical data they obtain is compromised due to the failure to adhere to our clinical protocols or regulatory requirements or for any other reasons, our clinical trials may be extended, delayed or terminated, and we may not be able to obtain regulatory approval for, or successfully commercialize, any product candidate that we develop. As a result, our financial results and the commercial prospects for any product candidate that we develop would be harmed, our costs could increase, and our ability to generate revenue could be delayed. While we will have agreements governing

their activities, our CROs will not be our employees, and we will not control whether or not they devote sufficient time and resources to our future clinical and preclinical programs. These CROs may also have relationships with other commercial entities, including our competitors, for whom they may also be conducting clinical trials, or other drug development activities which could harm our business. We face the risk of potential unauthorized disclosure or misappropriation of our intellectual property by CROs, which may reduce our trade secret protection and allow our potential competitors to access and exploit our proprietary technology.

If our relationship with any of these CROs terminates, we may not be able to enter into arrangements with alternative CROs or do so on commercially reasonable terms. Switching or adding additional CROs involves substantial cost and requires management time and focus. In addition, there is a natural transition period when a new CRO commences work. As a result, delays occur, which can negatively impact our ability to meet our desired clinical development timelines. While we intend to carefully manage our relationships with our CROs, there can be no assurance that we will not encounter challenges or delays in the future or that these delays or challenges will not have a negative impact on our business, financial condition and prospects.

In addition, 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. The FDA may conclude that a financial relationship between us and a principal investigator has created a conflict of interest or otherwise affected interpretation of the trial. The FDA 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 and may ultimately lead to the denial of marketing approval of our product candidates.

Risks Related to Our Intellectual Property

Licensing of intellectual property is of critical importance to our business and involves complex legal, business and scientific issues. If we breach our license agreements with Columbia University or any of the other agreements under which we acquired, or will acquire, the intellectual property rights to our product candidates, we could lose the ability to continue the development and commercialization of the related product.

The licensing of intellectual property is of critical importance to our business and to our current and future product candidates, and we expect to enter into additional such agreements in the future. In particular, our current product candidates AT-007, AT-001 and AT-003 are dependent on our license agreement with The Trustees of Columbia University in the City of New York, or Columbia University. Pursuant to that license agreement with Columbia University, or the 2016 Columbia Agreement, Columbia University granted us an exclusive license under two important patent families, and a nonexclusive license to certain know-how, owned by Columbia University to develop, manufacture or commercialize certain compounds, including AT-001, AT-003 and AT-007, for the diagnosis and treatment of human and animal diseases and conditions. The license grant is worldwide, with the exception of the patent family that covers AT-001 and AT-003. The license grant for the patent family that covers AT-001 and AT-003 excludes patent rights in China, Taiwan, Hong Kong and Macao, which Columbia University has exclusively licensed to a third party. We cannot prevent Columbia University's third party licensee from developing, manufacturing or commercializing certain compounds, including AT-001 and AT-003, but not including AT-007, in China, Taiwan, Hong Kong and Macao, and we cannot develop, manufacture or commercialize AT-001 or AT-003 in these territories, which could have a negative effect on our business.

We do not have the right to control the preparation, filing, prosecution and maintenance of patents and patent applications covering the technology that we license under either of the Columbia Agreements. Therefore, we cannot always be certain that these patents and patent applications will be prepared, filed, prosecuted and maintained in a manner consistent with the best interests of our business. Although we have a right to have our comments considered in connection with the prosecution process, if Columbia University fails to prosecute and maintain such patents, or loses rights to those patents or patent applications as a result of its control of the prosecution activities, the rights we have licensed may be reduced or eliminated, and our right to develop and commercialize any of our product candidates that are the subject of such licensed rights could be adversely affected.

If we fail to meet our obligations under the Columbia Agreement in any material respect and fail to cure such breach in a timely fashion, then Columbia University may terminate the Columbia Agreement. If the Columbia Agreement is terminated, and we lose our intellectual property rights under the Columbia Agreement, this may result in complete termination of our product development and any commercialization efforts for the product candidates that are subject to the agreement, including AT-007, AT-001, and AT-003. While we would expect to exercise all rights and remedies available to us, including seeking to cure any breach by us, and otherwise seek to preserve our rights under the Columbia Agreement, we may not be able to do so in a timely manner, at an acceptable cost or at all.

Furthermore, license agreements we enter into in the future may not provide exclusive rights to use intellectual property and technology in all relevant fields of use and in all territories in which we may wish to develop or commercialize our technology and products. As a result, we may not be able to prevent competitors from developing and commercializing competitive products in territories included in all of our licenses.

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

Our success depends, in large part, on our ability to obtain and maintain patent protection in the United States and other countries with respect to our product candidates and our technology. We and our licensors have sought, and intend to seek, to protect our proprietary position by filing patent applications in the United States and abroad related to our product candidates and our technology that are important to our business.

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. As a result, the issuance, scope, validity, enforceability and commercial value of our patent rights are highly uncertain. Our pending and future patent applications may not result in patents being issued which protect our technology or product candidates or which effectively prevent others from commercializing competitive technologies and product candidates. Since patent applications in the United States and most other countries are confidential for a period of time after filing, and some remain so until issued, we cannot be certain that we or our licensors were the first to file a patent application relating to any particular aspect of a product candidate. Furthermore, if third parties have filed such patent applications, an interference proceeding in the United States can be initiated by such third party, or by the U.S. Patent and Trademark Office, or USPTO, itself, to determine who was the first to invent any of the subject matter covered by the patent claims of our applications.

The patent prosecution process is expensive, time-consuming and complex, and we may not be able to file, prosecute, maintain, enforce or license all necessary or desirable patent applications at a reasonable cost or in a timely manner. It is also possible that we will fail to identify patentable aspects of our research and development output before it is too late to obtain patent protection.

We or our licensors have not pursued or maintained, and may not pursue or maintain in the future, patent protection for our product candidates in every country or territory in which we may sell our products, if approved. 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 infringing our patents in all countries outside the United States, or from selling or importing products that infringe our patents in and into the United States or other jurisdictions.

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 the patent applications we license or own do 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. Our competitors or other third parties may be able to circumvent our patents by developing similar or alternative products in a non-infringing manner.

The issuance of a patent is not conclusive as to its inventorship, scope, validity or enforceability, and our patents may be challenged in the courts or patent offices in the United States and abroad. Such challenges may result in 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 technology and product candidates. 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 intellectual property may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours.

Furthermore, our owned and in-licensed patents may be subject to a reservation of rights by one or more third parties. For example, the research resulting in certain of our owned and in-licensed patent rights and technology was funded in part by the U.S. government. As a result, the government may have certain rights, or march-in rights, to such patent rights and technology. When new technologies are developed with government funding, the government generally obtains certain rights in any resulting patents, including a nonexclusive license authorizing the government to use the invention for noncommercial purposes. These rights may permit the government to disclose our confidential information to third parties and to exercise march-in rights to use or allow third parties to use our licensed technology. The government can exercise its march-in rights if it determines that action is necessary because we fail to achieve practical application of the government-funded technology, because action is necessary to alleviate health or safety needs, to meet requirements of federal regulations, or to give preference to U.S. industry. In addition, our rights in such inventions may be subject to certain requirements to manufacture products embodying such inventions in the United States. Any exercise by the government of such rights could harm our competitive position, business, financial condition, results of operations and prospects.

Obtaining and maintaining our patent rights depends on compliance with various procedural, document submission, fee payment and other requirements imposed by government patent agencies, and our patent protection could be reduced or eliminated for noncompliance with these requirements.

The USPTO and various foreign governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other similar provisions during the patent application process. In addition, periodic maintenance fees, renewal fees, annuity fees and various other government fees on patents and/or patent applications will have to be paid to the USPTO and various government patent agencies outside the United States over the lifetime of our owned and licensed patents and/or applications and any patent rights we may own or license in the future. We rely on our service providers or our licensors to pay these fees. The USPTO and various non-U.S. government patent agencies require compliance with several 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 we are also dependent on our licensors to take the necessary action to comply with these requirements with respect to our licensed intellectual property. Noncompliance events that could result in abandonment or lapse of a patent or patent application include, but are not limited to, failure to respond to official actions within prescribed time limits, nonpayment of fees and failure to properly legalize and submit formal documents. If we or our licensors fail to maintain the patents and patent applications covering our products or technologies, we may not be able to stop a competitor from marketing products that are the same as or similar to our product candidates, which would have an adverse effect on our business. In many cases, an inadvertent lapse can be cured by payment of a late fee or by other means in accordance with the applicable rules. There are situations, however, 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. In such an event, potential competitors might be able to enter the market and this circumstance could harm our business.

In addition, if we fail to apply for applicable patent term extensions or adjustments, we will have a more limited time during which we can enforce our granted patent rights. In addition, if we are responsible for patent prosecution and maintenance of patent rights in-licensed to us, any of the foregoing could expose us to liability to the applicable patent owner.

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

Given the amount of time required for the development, testing and regulatory review of product candidates such as AT-007, AT-001, and AT-003, patents protecting such candidates might expire before or shortly after such candidates are commercialized. We expect to seek extensions of patent terms in the United States and, if available, in other countries where we have or will obtain patent rights. In the United States, the Drug Price Competition and Patent Term Restoration Act of 1984 permits a patent term extension of up to five years beyond the normal expiration of the patent; provided that the patent is not enforceable for more than 14 years from the date of drug approval, which is limited to the approved indication (or any additional indications approved during the period of extension). Furthermore, only one patent per approved product can be extended and only those claims covering the approved product, a method for using it or a method for manufacturing it may be extended. However, the applicable authorities, including the FDA and the USPTO in the United States, and any equivalent regulatory authority in other countries, may not agree with our assessment of whether such extensions are available, and may refuse to grant extensions to our patents, or may grant more limited extensions than we request. If this occurs, our competitors may be able to take advantage of our investment in development and clinical trials by referencing our clinical and preclinical data and launch their drug earlier than might otherwise be the case.

Third-parties may initiate legal proceedings alleging that we are infringing, misappropriating or otherwise violating their intellectual property rights, the outcome of which would be uncertain and could have a negative impact on the success of our business.

Our commercial success depends, in part, upon our ability and the ability of others with whom we may collaborate to develop, manufacture, market and sell our current and any future product candidates and use our proprietary technologies without infringing, misappropriating or otherwise violating the proprietary rights and intellectual property of third parties. The biotechnology and pharmaceutical industries are characterized by extensive and complex litigation regarding patents and other intellectual property rights. We may in the future become party to, or be threatened with, adversarial proceedings or litigation regarding intellectual property rights with respect to our current and any future product candidates and technology, including interference proceedings, post grant review and inter partes review before the USPTO. Third parties may assert infringement claims against us based on existing patents or patents that may be granted in the future, regardless of their merit. There is a risk that third parties may choose to engage in litigation with us to enforce or to otherwise assert their patent rights against us. Even if we believe such claims are without merit, a court of competent jurisdiction could hold that these third-party patents are valid, enforceable and infringed, which could have a negative impact on our ability to commercialize our current and any future product candidates. In order to successfully challenge the validity of any such U.S. patent in federal court, we would need to overcome a presumption of validity. As this is a high burden and requires us to present clear and convincing evidence as to the invalidity of any such U.S. patent claim, there is no assurance that a court of competent jurisdiction would invalidate the claims of any such U.S. patent. Moreover, given the vast number of patents in our field of technology, we cannot be certain that we do not infringe existing patents or that we will not infringe patents that may be granted in the future. Other companies and research institutions have filed, and may file in the future, patent applications related to AR inhibitors and their therapeutic use. Some of these patent applications have already been allowed or issued, and others may issue in the future. While we may decide to initiate proceedings to challenge the validity of these or other patents in the future, we may be unsuccessful, and courts or patent offices in the United States and abroad could uphold the validity of any such patent. Furthermore, because patent applications can take many years to issue and may be confidential for 18 months or more after filing, and because pending patent claims can be revised before issuance, there may be applications now pending which may later result in issued patents that may be infringed by the manufacture, use or sale of our product candidates. Regardless of when filed, we may fail to identify relevant third-party patents or patent applications, or we may incorrectly conclude that a third-party patent is invalid or not infringed by our product candidates or activities. If a patent holder believes that our product candidate infringes its patent, the patent holder may sue us even if we have received patent protection for our technology. Moreover, we may face patent infringement claims from nonpracticing entities that have no relevant drug revenue and against whom our own patent portfolio may thus have no deterrent effect. If a patent infringement suit were threatened or brought against us, we could be forced to stop or delay research, development, manufacturing or sales of the drug or product candidate that is the subject of the actual or threatened suit.

If we are found to infringe a third party's valid and enforceable intellectual property rights, we could be required to obtain a license from such third party to continue developing, manufacturing and marketing our product candidate(s) and technology. Under any such license, we would most likely be required to pay various types of fees, milestones, royalties or other amounts. Moreover, we may not be able to obtain any required license on commercially reasonable terms or at all.

The licensing or acquisition of third-party intellectual property rights is a competitive area, and more established companies may also pursue strategies to license or acquire third-party intellectual property rights that we may consider attractive or necessary. These established companies may have a competitive advantage over us due to their size, capital resources and greater clinical development and commercialization capabilities. In addition, companies that perceive us to be a competitor may be unwilling to assign or license rights to us. We also may be unable to license or acquire third-party intellectual property rights on terms that would allow us to make an appropriate return on our investment or at all. If we are unable to successfully obtain rights to required third-party intellectual property rights or maintain the existing intellectual property rights we have, we may have to abandon development of the relevant program or product candidate, which could have an adverse effect on our business, financial condition, results of operations and prospects. Furthermore, even if we were able to obtain a license, it could be nonexclusive, thereby giving our competitors and other third-parties access to the same technologies licensed to us, and it could require us to make substantial licensing and royalty payments. We could be forced, including by court order, to cease developing, manufacturing and commercializing the infringing technology or product candidate. In addition, we could be found liable for monetary damages, including treble damages and attorneys' fees, if we are found to have willfully infringed a patent or other intellectual property right. We may be required to indemnify collaborators or contractors against such claims. A finding of infringement could prevent us from manufacturing and commercializing our current or any future product candidates or force us to cease some or all of our business operations, which could harm our business. Even if we are successful in defending against such claims, litigation can be expensive and time-consuming and would divert management's attention from our core business. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation. There could also be public announcements of the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, it could have an adverse effect on the price of our common stock.

Claims that we have misappropriated the confidential information or trade secrets of third parties could have a similar negative impact on our business, financial condition, results of operations and prospects.

We may be subject to claims asserting that our employees, consultants or advisors have wrongfully used or disclosed alleged trade secrets of their current or former employers or claims asserting ownership of what we regard as our own intellectual property.

Certain of our employees, consultants or advisors are currently, or were previously, employed at universities or other biotechnology or pharmaceutical companies, including our competitors or potential competitors. Although we try to ensure that our employees, consultants and advisors do not use the proprietary information or know-how of others in their work for us, we may be subject to claims that these individuals or we have used or disclosed intellectual property, including trade secrets or other proprietary information, of any such individual's current or former employer. 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. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management.

In addition, we may in the future be subject to claims by our former employees or consultants asserting an ownership right in our patents or patent applications, as a result of the work they performed on our behalf. Although 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, and we cannot be certain that our agreements with such parties will be upheld in the face of a potential challenge or that they will not be breached, for which we may not have an adequate remedy. 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.

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

Competitors may infringe, misappropriate or otherwise violate our patents, the patents of our licensors or our other intellectual property rights. To counter infringement or unauthorized use, we may be required to file legal claims, which can be expensive and time-consuming and are likely to divert significant resources from our core business, including distracting our technical and management personnel from their normal responsibilities. In addition, in an infringement proceeding, a court may decide that a patent of ours or our licensors is not valid or is unenforceable, or may refuse to stop the other party from using the technology at issue on the grounds that our patents do not cover the technology in question. An adverse result in any litigation or defense proceedings could put one or more of our owned or licensed patents at risk of being invalidated or interpreted narrowly and could put our owned or licensed patent applications at risk of not issuing. The initiation of a claim against a third party might also cause the third-party to bring counterclaims against us, such as claims asserting that our patent rights are invalid or unenforceable. In patent litigation in the United States, defendant counterclaims alleging invalidity or unenforceability are commonplace. Grounds for a validity challenge could be an alleged failure to meet any of several statutory requirements, including lack of novelty, obviousness, non-enablement or lack of statutory subject matter. Grounds for an unenforceability assertion could be an allegation that someone connected with prosecution of the patent withheld relevant material information from the USPTO, or made a materially misleading statement, during prosecution. Third parties may also raise similar validity claims before the USPTO in post-grant proceedings such as ex parte reexaminations, inter partes review, post-grant review, or oppositions or similar proceedings outside the United States, in parallel with litigation or even outside the context of litigation. The outcome following legal assertions of invalidity and unenforceability is unpredictable. We cannot be certain that there is or will be no invalidating prior art, of which we and the patent examiner were unaware during prosecution. For the patents and patent applications that we have licensed, we may have limited or no right to participate in the defense of any licensed patents against challenge by a third party. If a defendant were to prevail on a legal assertion of invalidity or unenforceability, we would lose at least part, and perhaps all, of any future patent protection on our current or future product candidates. Such a loss of patent protection could harm our business.

We may not be able to prevent, alone or with our licensors, misappropriation of our intellectual property rights, particularly in countries where the laws may not protect those rights as fully as in the United States. Our business could be harmed if in litigation the prevailing party does not offer us a license, or if the license offered as a result is not on commercially reasonable terms. Any litigation or other proceedings to enforce our intellectual property rights may fail, and even if successful, may result in substantial costs and distract our management and other employees.

Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation. There could also be public announcements of the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, it could have an adverse effect on the price of our common stock.

We may not have sufficient financial or other resources to adequately conduct such litigation or proceedings. Some of our competitors may be able to sustain the costs of such litigation or proceedings more effectively than we can because of their greater financial resources and more mature and developed intellectual property portfolios. Accordingly, despite our efforts, we may not be able to prevent third parties from infringing upon or misappropriating or from successfully challenging our intellectual property rights. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could have an adverse effect on our ability to compete in the marketplace.

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

Changes in either the patent laws or interpretation of the patent laws in the United States could increase the uncertainties and costs surrounding the prosecution of patent applications and the enforcement or defense of issued

patents. Assuming that other requirements for patentability are met, prior to March 2013, in the United States, the first to invent the claimed invention was entitled to the patent, while outside the United States, the first to file a patent application was entitled to the patent. After March 2013, under the Leahy-Smith America Invents Act, or the America Invents Act, the United States transitioned to a first inventor to file system in which, assuming that other requirements for patentability are met, the first inventor to file a patent application will be entitled to the patent on an invention regardless of whether a third-party was the first to invent the claimed invention. The America Invents Act also includes a number of significant changes that affect the way patent applications are 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 post-grant review, *inter partes* review, and derivation proceedings. However, the America Invents Act and its implementation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our issued patents, all of which could have an adverse effect on our business, financial condition, results of operations, and prospects.

In addition, 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 actions by the U.S. Congress, the federal courts, and the USPTO, the laws and regulations governing patents could change in unpredictable ways that could weaken our ability to obtain new patents or to enforce patents that we own, have licensed or might obtain in the future. Similarly, changes in patent law and regulations in other countries or jurisdictions, changes in the governmental bodies that enforce them or changes in how the relevant governmental authority enforces patent laws or regulations may weaken our ability to obtain new patents or to enforce patents that we own or have licensed or that we may obtain in the future.

We may not be able to protect our intellectual property rights throughout the world, which could negatively impact our business.

Filing, prosecuting and defending patents covering our current and any future product candidates in all countries throughout the world would be prohibitively expensive. Competitors may use our technologies in jurisdictions where we or our licensors have not obtained patent protection to develop their own products and, further, may export otherwise infringing products to territories where we may obtain patent protection but where patent enforcement is not as strong as that in the United States. These products may compete with our products in jurisdictions where we do not have any issued or licensed patents, and any future patent claims or other intellectual property rights may not be effective or sufficient to prevent them from so competing.

Many companies have encountered significant problems in protecting and defending intellectual property rights in foreign jurisdictions. The legal systems of certain countries, particularly certain developing countries, do not favor the enforcement of patents, trade secrets and other intellectual property protection, particularly those relating to biotechnology products, which could make it difficult for us to stop the infringement of our patents or marketing of competing products in violation of our intellectual property and proprietary rights generally. Proceedings to enforce our intellectual property and proprietary rights in foreign jurisdictions could result in substantial costs and divert our efforts and attention from other aspects of our business, could put our patents at risk of being invalidated or interpreted narrowly, could put our patent applications 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 and proprietary 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 or any of our licensors is 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.

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

Since we rely on third parties to help us discover, develop and manufacture our current and any future product candidates, or if we collaborate with third parties for the development, manufacturing or commercialization of our current or any future product candidates, we must, at times, share trade secrets with them. We may also conduct joint research and development programs that may require us to share trade secrets under the terms of our research and development partnerships or similar agreements. We seek to protect our proprietary technology in part by entering into confidentiality agreements and, if applicable, material transfer agreements, consulting agreements or other similar agreements with our advisors, employees, third-party contractors and consultants prior to beginning research or disclosing proprietary information. These agreements typically limit the rights of the third parties to use or disclose our confidential information, including our trade secrets. Despite the contractual provisions employed when working with third parties, the need to share trade secrets and other confidential information increases the risk that such trade secrets become known by our competitors, are inadvertently incorporated into the technology of others, or are disclosed or used in violation of these agreements. Given that our proprietary position is based, in part, on our know-how and trade secrets, a competitor's discovery of our trade secrets or other unauthorized use or disclosure could have an adverse effect on our business and results of operations.

In addition, these agreements typically restrict the ability of our advisors, employees, third-party contractors and consultants to publish data potentially relating to our trade secrets. Despite our efforts to protect our trade secrets, we may not be able to prevent the unauthorized disclosure or use of our technical know-how or other trade secrets by the parties to these agreements. Moreover, we cannot guarantee that we have entered into such agreements with each party that may have or have had access to our confidential information or proprietary technology and processes. Monitoring unauthorized uses and disclosures is difficult, and we do not know whether the steps we have taken to protect our proprietary technologies will be effective. If any of the collaborators, scientific advisors, employees, contractors and consultants who are parties to these agreements breaches or violates the terms of any of these agreements, we may not have adequate remedies for any such breach or violation, and we could lose our trade secrets as a result. Moreover, if confidential information that is licensed or disclosed to us by our partners, collaborators, or others is inadvertently disclosed or subject to a breach or violation, we may be exposed to liability to the owner of that confidential information. Enforcing a claim that a third-party illegally or unlawfully obtained and is using our trade secrets, like patent litigation, is expensive and time-consuming, and the outcome is unpredictable. In addition, courts outside the United States are sometimes less willing to protect trade secrets.

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

In addition to seeking patent and trademark protection for our product candidates, we also rely on trade secrets, including unpatented know-how, technology and other proprietary information, to maintain our competitive position. We seek to protect our trade secrets, in part, by entering into nondisclosure and confidentiality agreements with parties who have access to them, such as our employees, corporate collaborators, outside scientific collaborators, contract manufacturers, consultants, advisors and other third parties. We also enter into confidentiality and invention or patent assignment agreements with our employees, advisors and consultants. Despite these efforts, any of these parties may breach the agreements and disclose our proprietary information, including our trade secrets. Monitoring unauthorized uses and disclosures of our intellectual property is difficult, and we do not know whether the steps we have taken to protect our intellectual property will be effective. In addition, we may not be able to obtain adequate remedies for any 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, our competitors may independently develop knowledge, methods and know-how equivalent to our trade secrets. Competitors could purchase our products and replicate some or all of the competitive advantages we derive

from our development efforts for technologies on which we do not have patent protection. If any of our trade secrets were to be lawfully obtained or independently developed by a competitor, we would have no right to prevent them, or those to whom they communicate it, from using that technology or information to compete with us. If any of our trade secrets were to be disclosed to or independently developed by a competitor, our competitive position would be harmed.

We also seek to preserve the integrity and confidentiality of our data and other confidential information by maintaining physical security of our premises and physical and electronic security of our information technology systems. While we have confidence in these individuals, organizations and systems, agreements or security measures may be breached, and detecting the disclosure or misappropriation of confidential information and enforcing a claim that a party illegally disclosed or misappropriated confidential information is difficult, expensive and time-consuming, and the outcome is unpredictable. Further, we may not be able to obtain adequate remedies for any breach. In addition, our confidential information may otherwise become known or be independently discovered by competitors, in which case we would have no right to prevent them, or those to whom they communicate it, from using that technology or information to compete with us.

Any trademarks we may obtain may be infringed or successfully challenged, resulting in harm to our business.

We expect to rely on trademarks as one means to distinguish any of our product candidates that are approved for marketing from the products of our competitors. We have selected trademarks for some of our later stage product candidates and filed applications to register those trademarks for our current or any future product candidates. For other earlier stage product candidates, we have not yet selected trademarks or begun the process of applying to register trademarks. Our pending trademark applications, and any future trademark applications may not be approved. Third parties may oppose our trademark applications or otherwise challenge our use of the trademarks. In the event that our trademarks are successfully challenged, we could be forced to rebrand our products, which could result in loss of brand recognition and could require us to devote resources to advertising and marketing new brands. Our competitors may infringe our trademarks, and we may not have adequate resources to enforce our trademarks.

In addition, any proprietary name we propose to use with our current or any other product candidate in the United States must be approved by the FDA, regardless of whether we have registered it, or applied to register it, as a trademark. The FDA typically conducts a review of proposed product names, including an evaluation of the potential for confusion with other product names. If the FDA objects to any of our proposed proprietary product names, we may be required to expend significant additional resources in an effort to identify a suitable proprietary product name that would qualify under applicable trademark laws, not infringe the existing rights of third parties and be acceptable to the FDA.

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

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. The following examples are illustrative:

- others may be able to make compounds or formulations that are similar to our product candidates but that are not covered by the claims of any patents, should they issue, that we own or license;
- we or our licensors might not have been the first to make the inventions covered by the issued patents or pending patent applications that we own or license;
- we or our licensors 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 our pending patent applications will not lead to issued patents;
- issued patents that we own or license may not provide us with any competitive advantages, or may be held invalid or unenforceable as a result of legal challenges;
- our competitors might conduct research and development activities in the United States and other countries that provide a safe harbor from patent infringement claims for certain research and development activities,

as well as in countries where we do not have patent rights, and then use the information learned from such activities to develop competitive drugs for sale in our major commercial markets;
- we may not develop additional proprietary technologies that are patentable; and
- the patents of others may have an adverse effect on our business.

Risks Related to Our Business Operations, Employee Matters and Managing Growth

We are highly dependent on the services of our Chief Executive Officer and Chairman, Dr. Shoshana Shendelman, and our Chief Medical Officer, Dr. Riccardo Perfetti, and if we are not able to retain these members of our management team or recruit and retain additional management, clinical and scientific personnel, our business will be harmed.

We are highly dependent on our Chief Executive Officer and Chairman, Dr. Shoshana Shendelman, and our Chief Medical Officer, Dr. Riccardo Perfetti. Each of them may currently terminate their employment with us at any time. The loss of the services of either of these persons could impede the achievement of our research, development and commercialization objectives.

Recruiting and retaining other senior executives, qualified scientific and clinical personnel and, if we progress the development of any of our product candidates, commercialization, manufacturing and sales and marketing personnel, will be critical to our success. The loss of the services of our executive officers or other key employees could impede the achievement of our research, development and commercialization objectives and seriously harm our ability to successfully implement our business strategy. Furthermore, replacing executive officers and key employees may be difficult and may take an extended period of time because of the limited number of individuals in our industry with the breadth of skills and experience required to successfully develop, gain regulatory approval of and commercialize our product candidates. Competition to hire from this limited pool is intense, and we may be unable to hire, train, retain or motivate these key personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies for similar personnel. We also experience competition for the hiring of scientific and clinical personnel from universities and research institutions. In addition, we rely on consultants and advisors, including scientific and clinical advisors, to assist us in formulating our research and development and commercialization strategy. Our consultants and advisors may have commitments under consulting or advisory contracts with other entities that may limit their availability to us. If we are unable to continue to attract and retain high-quality personnel, our ability to pursue our growth strategy will be limited.

Our future performance will also depend, in part, on our ability to successfully integrate newly hired executive officers into our management team and our ability to develop an effective working relationship among senior management. Our failure to integrate these individuals and create effective working relationships among them and other members of management could result in inefficiencies in the development and commercialization of our product candidates, harming future regulatory approvals, sales of our product candidates and our results of operations. Additionally, we do not currently maintain "key person" life insurance on the lives of our executives or any of our employees.

We expect to expand our organization, and we may experience difficulties in managing this growth, which could disrupt our operations.

As of December 31, 2022, we had 27 full-time employees. As the clinical development of our product candidates progresses, we also expect to experience significant growth in the number of our employees and the scope of our operations, particularly in the areas of research, drug development, 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, 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. Any inability to manage growth could delay the execution of our business plans or disrupt our operations.

Our internal computer systems, or those of our collaborators or other contractors or consultants, may fail or suffer security breaches, which could result in a significant disruption of our product development programs and our ability to operate our business effectively, and adversely affect our business and operating results.

Our internal computer systems, cloud-based computing services and those of our current and any future collaborators and other contractors or consultants are vulnerable to damage or interruption from computer viruses, data corruption, cyber-based attacks (including phishing attempts, denial of service attacks, and malware or ransomware incidents), unauthorized access, natural disasters, terrorism, war, international hostilities and telecommunication and electrical failures. While we have not experienced any significant system failure, accident or security breach to date, if such an event were to occur and cause interruptions in our operations, it could result in a disruption of our development programs and our business operations, whether due to a loss of our trade secrets or other proprietary information or other similar disruptions. For example, the loss of clinical trial data from completed or future clinical trials could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. Furthermore, federal, state and international laws and regulations, such as the European Union's General Data Protection Regulation, which took effect in May 2018, can expose us to enforcement actions and investigations by regulatory authorities, and potentially result in regulatory penalties and significant legal liability, if our information technology security efforts fail. In addition, our software systems include cloud-based applications that are hosted by third-party service providers with security and information technology systems subject to similar risks. To the extent that any disruption or security breach were to result in a loss of, or damage to, our data or applications, or inappropriate disclosure of confidential or proprietary information, we could incur liability, our competitive position could be harmed and the further development and commercialization of our product candidates could be delayed.

Risks of unauthorized access and cyber-attacks have increased as most of our personnel, and the personnel of many third-parties with which we do business, have adopted remote working arrangements as a result of the Covid-19 pandemic, and may increase as a result of recent hostilities between Russia and Ukraine. Improper or inadvertent employee behavior, including data privacy breaches by employees, contractors and others with permitted access to our systems, may also pose a risk that sensitive data may be exposed to unauthorized persons or to the public. If a system failure or security breach occurs and interrupts our operations or the operations at one of our third-party vendors, it could result in intellectual property and other proprietary or confidential information being lost or stolen or a material disruption of our drug development programs. For example, the loss of clinical trial data from ongoing or planned clinical trials could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any disruption or security breach results in a loss of or damage to our data or applications, loss of trade secrets or inappropriate disclosure of confidential or proprietary information, including protected health information or personal data of employees or former employees, access to our clinical data, or disruption of the manufacturing process, we could incur liability and the further development of our drug candidates could be delayed. We may also be vulnerable to cyber-attacks by hackers or other malfeasance. This type of breach of our cybersecurity may compromise our confidential information and/or our financial information and adversely affect our business or reputation or result in legal or regulatory proceedings. In addition, if a ransomware attack or other cyber-attack occurs, either internally or at our third-party vendors, it is possible we could be prevented from accessing our systems or data, which may cause interruptions or delays in our business, cause us to incur remediation costs or subject us to demands to pay ransom, or adversely affect our business reputation.

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

We are exposed to the risk of fraud or other misconduct by our employees, principal investigators, consultants and commercial partners. Misconduct by these parties could include intentional failures to comply with FDA regulations or the regulations applicable in other jurisdictions, provide accurate information to the FDA and other regulatory authorities, comply with healthcare fraud and abuse laws and regulations in the United States and abroad, report financial information or data accurately or disclose unauthorized activities to us. In particular, sales, marketing and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, misconduct, kickbacks, self-dealing and other abusive practices. These laws and regulations restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs, and other business arrangements. Such misconduct also could involve the improper use of information obtained in the course of

clinical trials or interactions with the FDA or other regulatory authorities, which could result in regulatory sanctions and cause serious harm to our reputation. It is not always possible to identify and deter employee misconduct, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from government 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 result in significant civil, criminal and administrative penalties, damages, fines, disgorgement, imprisonment, exclusion from participating in government-funded healthcare programs, such as Medicare and Medicaid, additional reporting requirements and oversight if we become subject to a corporate integrity agreement or similar agreement to resolve allegations of noncompliance with these laws, contractual damages, reputational harm and the curtailment or restructuring of our operations, any of which could have a negative impact on our business, financial condition, results of operations and prospects.

Any future acquisitions or strategic collaborations may increase our capital requirements, dilute our stockholders, cause us to incur debt or assume contingent liabilities and/or subject us to other risks.

From time to time, we may evaluate various acquisitions and strategic collaborations, including licensing or acquiring complementary drugs, intellectual property rights, technologies or businesses, as deemed appropriate to carry out our business plan. Any potential acquisition or strategic partnership may entail numerous risks, including:

- increased operating expenses and cash requirements;
- the assumption of additional indebtedness or contingent or unknown liabilities;
- assimilation of operations, intellectual property and drugs of an acquired company, including difficulties associated with integrating new personnel;
- the diversion of our management's attention from our existing drug programs and initiatives in pursuing such a strategic partnership, merger or acquisition;
- retention of key employees, the loss of key personnel, and uncertainties in our ability to maintain key business relationships;
- risks and uncertainties associated with the other party to such a transaction, including the prospects of that party and their existing drugs or product candidates and regulatory approvals; and
- our inability to generate revenue from acquired technology and/or drugs sufficient to meet our objectives in undertaking the acquisition or even to offset the associated acquisition and maintenance costs.

In addition, if we engage in future acquisitions or strategic partnerships, we may issue dilutive securities, assume or incur debt obligations, incur large one-time expenses, and acquire intangible assets that could result in significant future amortization expense. Moreover, we may not be able to locate suitable acquisition opportunities, and this inability could impair our ability to grow or obtain access to technology or drugs that may be important to the development of our business.

Our business may be adversely affected by the coronavirus outbreak.

The Covid-19 pandemic, ("Covid-19") has had and may continue to have a material impact on our operations. Infections and deaths related to Covid-19 continue to disrupt the United States' healthcare and healthcare regulatory systems. Such disruptions could divert healthcare resources away from, or materially delay FDA approval with respect to, our clinical trials. In addition, other known and unknown factors caused by Covid-19 could materially delay our clinical trials, including our ability to recruit and retain patients and principal investigators and site staff who, as healthcare providers, may have heightened exposure to Covid-19. For example, with respect to our trials related to AT-001 for the treatment of Diabetic Cardiomyopathy, we have experienced, and may continue to experience, delays in patient enrollment. Furthermore, we may experience additional delays in patient enrollment that we may not be able to mitigate. In addition, we have partnered with clinical research organizations, or CROs, to conduct clinical studies in jurisdictions, such as the EU, that have been affected by the spread of Covid-19. There is a possibility that such CROs may become unavailable or that the clinical trials they manage may be delayed due to Covid-19 or containment efforts associated with it. Such events may lead to termination of our relationship with affected CROs, affecting the development and study of our product candidates. Any elongation or de-prioritization of our clinical trials or delay in regulatory review resulting from such disruptions could materially affect the development and study of our product

candidates, and increase the costs related to such development. While Covid-19 vaccines have become available both domestically and internationally, the effects of Covid-19, including the impacts described above may last longer than expected, extending such impacts, and materially impacting our business, financial condition, and results of operations.

Risks Related to Ownership of Our Common Stock

The market price of our common stock is volatile and has fluctuated substantially, which could result in substantial losses for purchasers of our common stock.

The stock market in general and the market for biopharmaceutical and pharmaceutical companies in particular, has experienced extreme volatility that has often been unrelated to the operating performance of particular companies. As a result of this volatility, you may not be able to sell your common stock at or above the price at which you purchased it. In addition to the factors discussed in this "Risk Factors" section and elsewhere in this Annual Report, the market price for our common stock has been, and is likely to continue to be influenced by the following:

- the commencement, enrollment, results of , or any delays in our planned or future clinical trials of our product candidates or those of our competitors;
- the success of competitive drugs or therapies;
- regulatory or legal developments in the United States and other countries;
- the success of competitive products or technologies;
- developments or disputes concerning patent applications, issued patents or other proprietary rights;
- the recruitment or departure of key personnel;
- the level of expenses related to our product candidates or clinical development programs;
- the results of our efforts to discover, develop, acquire or in-license additional product candidates;
- actual or anticipated changes in estimates as to financial results, development timelines or recommendations by securities analysts;
- our inability to obtain or delays in obtaining adequate drug supply for any approved drug or inability to do so at acceptable prices;
- disputes or other developments relating to proprietary rights, including patents, litigation matters and our ability to obtain patent protection for our technologies;
- the potential impact of the Covid-19 pandemic on the timing and progress of our ongoing clinical trials, our business, results of operations, liquidity, and operations and our ability to mitigate those potential impacts;
- significant lawsuits, including patent or stockholder litigation;
- variations in our financial results or those of companies that are perceived to be similar to us;
- changes in the structure of healthcare payment systems, including coverage and adequate reimbursement for any approved drug;
- market conditions in the pharmaceutical and biotechnology sectors;
- general economic, political, and market conditions and overall fluctuations in the financial markets in the United States and abroad; and
- investors' general perception of us and our business.

These and other market and industry factors have caused the market price and demand for our common stock to fluctuate substantially, regardless of our actual operating performance, which may limit or prevent investors from selling their shares at or above the price paid for the shares and may otherwise negatively affect the liquidity of our common stock. Furthermore, we believe our stock has been, and may in the future be, adversely affected as a result of actions by third-parties. 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.

Some companies that have experienced volatility in the trading price of their shares have been the subject of securities class action litigation. Any lawsuit to which we are a party, with or without merit, may result in an unfavorable judgment. We also may decide to settle lawsuits on unfavorable terms. Any such negative outcome could result in payments of substantial damages or fines, damage to our reputation or adverse changes to our business practices. Defending against litigation is costly and time-consuming, and could divert our management's attention and our

resources. Furthermore, during the course of litigation, there could be negative public announcements of the results of hearings, motions or other interim proceedings or developments, which could have a negative effect on the market price of our common stock.

Concentration of ownership of our common stock among our existing executive officers, directors and principal stockholders may prevent new investors from influencing significant corporate decisions.

Based upon shares of our common stock outstanding as of December 31, 2022, our executive officers, directors and stockholders who owned more than 10% of our outstanding common stock, in the aggregate, beneficially own shares representing approximately 40.1% of our outstanding common stock. If our executive officers, directors and stockholders who owned more than 10% of our outstanding common stock acted together, they may be able to significantly influence all matters requiring stockholder approval, including the election and removal of directors and approval of any merger, consolidation or sale of all or substantially all of our assets. The concentration of voting power and transfer restrictions could delay or prevent an acquisition of our company on terms that other stockholders may desire or result in the management of our company in ways with which other stockholders disagree.

Because we do not anticipate paying any cash dividends on our capital stock in the foreseeable future, capital appreciation, if any, will be your sole source of gain.

You should not rely on an investment in our common stock to provide dividend income. We have never declared or paid cash dividends on our capital stock. We currently intend to retain all of our future earnings, if any, to finance the growth and development of our business. In addition, the terms of any future debt agreements may preclude us from paying dividends. As a result, capital appreciation, if any, of our common stock will be your sole source of gain for the foreseeable future. Investors seeking cash dividends should not purchase our common stock.

Future sales of common stock by holders of our common stock, or the perception that such sales may occur, could depress the market price of our common stock.

Sales of a substantial number of shares of our common stock in the public market could occur at any time, subject to certain restrictions described below. These sales, or the perception in the market that holders of a large number of shares intend to sell shares, could reduce the market price of our common stock. As of December 31, 2022, we had outstanding 48,063,358 shares of common stock. A substantial number of such shares are currently restricted as a result of securities laws or lock-up agreements but will be able to be sold in the future.

We further have registered all shares of common stock that we may issue in the future or have issued to date under our equity compensation plans. These shares can be freely sold in the public market upon issuance, subject to volume limitations applicable to affiliates and certain lock-up agreements. Sales of a large number of the shares issued under these plans in the public market could have an adverse effect on the market price of our common stock.

If we fail to regain compliance with the continued listing requirements of Nasdaq, our common stock may be delisted and the price of our common stock and our ability to access the capital markets could be negatively impacted.

On November 15, 2022, we received a deficiency letter from the staff of the Listing Qualifications Department of the Nasdaq Stock Market, or Nasdaq, notifying us that we were not in compliance with Listing Rule 5450(b)(1)(A), which requires a minimum of $10 million in stockholders' equity, for companies listed under the NASDAQ Global Market, referred to as the equity rule. On February 24, 2023, the Nasdaq staff granted us an extension to regain compliance with the equity rule, or to transition to the NASDAQ Capital Market, which has a lower stockholders' equity requirement, by May 15, 2023. We intend to enter into one or more financing transactions in an effort to comply with the equity rule and may, if appropriate, consider other available options.

There are many factors that may adversely affect our stockholders' equity, including those described throughout this section titled "Risk Factors." Many of these factors are outside of our control. As a result, we may not be able to regain, or once regained, sustain compliance with the equity rule or other Nasdaq rule market cap requirements in the

long term. Any potential delisting of our common stock from the Nasdaq Global Market would likely result in decreased liquidity and increased volatility for our common stock and would adversely affect our ability to raise additional capital or to enter into strategic transactions. Any potential delisting of our common stock from the Nasdaq Global Market would also make it more difficult for our stockholders to sell our common stock in the public market.

General Risk Factors

If research analysts do not publish research or reports, or publish unfavorable research or reports, about us, our business or our market, our stock price and trading volume could decline.

The trading market for our common stock will be influenced by the research and reports that industry or financial analysts publish about us or our business. Equity research analysts may discontinue research coverage of our common stock, and such lack of research coverage may adversely affect the market price of our common stock. We do not have any control over the analysts or the content and opinions included in their reports. The price of our shares could decline if one or more equity research analysts downgrade our shares or issue other unfavorable commentary or research about us. If one or more equity research analysts cease coverage of us or fail to publish reports on us regularly, demand for our shares could decrease, which in turn could cause the trading price or trading volume of our common stock to decline.

We have broad discretion in the use of our cash and cash equivalents and may use them ineffectively, in ways with which you do not agree or in ways that do not increase the value of your investment.

Our management has broad discretion in the application of our cash and cash equivalents, and could spend the proceeds in ways that do not improve our results of operations or enhance the value of our common stock. The failure by our management to apply these funds effectively could result in additional operating losses that could have a negative impact on our business, cause the price of our common stock to decline and delay the development of our product candidates. Pending their use, we may invest our cash and cash equivalents in a manner that does not produce income or that loses value.

We are an "emerging growth company," and the reduced disclosure requirements applicable to emerging growth companies may make our common stock less attractive to investors.

We are an "emerging growth company," or EGC, as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act, and we intend to take advantage of some of the exemptions from reporting requirements that are applicable to other public companies that are not EGCs, including:

- being permitted to provide only two years of audited financial statements, in addition to any required unaudited interim financial statements, with correspondingly reduced "Management's Discussion and Analysis of Financial Condition and Results of Operations" disclosure;
- not being required to comply with the auditor attestation requirements in the assessment of our internal control over financial reporting;
- not being required to comply with any requirement that may be adopted by the Public Company Accounting Oversight Board regarding mandatory audit firm rotation or a supplement to the auditor's report providing additional information about the audit and the financial statements;
- reduced disclosure obligations regarding executive compensation; and
- not being required to hold a nonbinding advisory vote on executive compensation and stockholder approval of any golden parachute payments not previously approved.

We cannot predict whether investors will find our common stock less attractive because we will 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. We currently take advantage of some or all of these reporting exemptions until we are no longer an EGC. We will remain an EGC until the earlier of (i) December 31, 2024, (ii) the last day of the fiscal year in which we have total annual gross revenue of at least $1.235 billion, (iii) the last day of the first fiscal year in which we are deemed to be a large accelerated filer, which means the market value of our

common stock that is held by non-affiliates exceeds $700 million as of the prior June 30th, and (iv) the date on which we have issued more than $1.0 billion in non-convertible debt during the prior three-year period.

In addition, under Section 107(b) of the JOBS Act, EGCs can delay adopting new or revised accounting standards until such time as those standards apply to private companies. We have irrevocably elected not to avail ourselves of this exemption from new or revised accounting standards and, therefore, we will be subject to the same requirements to adopt new or revised accounting standards as other public companies that are not EGCs.

We have incurred 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.

As a public company, and particularly after we are no longer an EGC, we incur and will continue to incur significant legal, accounting and other expenses. In addition, the Sarbanes-Oxley Act of 2002, or the Sarbanes-Oxley Act, and rules subsequently implemented by the SEC and The Nasdaq Stock Market LLC have imposed 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 comply with these requirements. Moreover, these rules and regulations increase our legal and financial compliance costs and 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.

Pursuant to Section 404 of the Sarbanes-Oxley Act, or Section 404, we will be required to furnish a report by our management on our internal control over financial reporting, including an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. However, while we remain an EGC, we will not be required to include an attestation report on internal control over financial reporting issued by our independent registered public accounting firm. 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. Despite our efforts, there is a risk that neither we nor our independent registered public accounting firm will be able to conclude within the prescribed timeframe that our internal control over financial reporting is effective as required by Section 404. This could result in an adverse reaction in the financial markets due to a loss of confidence in the reliability of our financial statements.

Provisions in our corporate charter documents and under Delaware law could make an acquisition of us, which may be beneficial to our stockholders, more difficult and may prevent attempts by our stockholders to replace or remove our current management.

Provisions in our corporate charter and our bylaws may discourage, delay or prevent a merger, acquisition or other change in control of us that stockholders may consider favorable, including transactions in which you might otherwise receive a premium for your shares. These provisions also could limit the price that investors might be willing to pay in the future for shares of our common stock, thereby depressing the market price of our common stock. In addition, because our board of directors is responsible for appointing the members of our management team, these provisions may frustrate or prevent any attempts by our stockholders to replace or remove our current management by making it more difficult for stockholders to replace members of our board of directors. Among other things, these provisions:

- establish a classified board of directors such that not all members of the board are elected at one time;
- allow the authorized number of our directors to be changed only by resolution of our board of directors;
- limit the manner in which stockholders can remove directors from the board;
- establish advance notice requirements for stockholder proposals that can be acted on at stockholder meetings and nominations to our board of directors;

- require that stockholder actions must be effected at a duly called stockholder meeting and prohibit actions by our stockholders by written consent;
- limit who may call stockholder meetings;
- authorize our board of directors to issue preferred stock without stockholder approval, which could be used to institute a stockholder rights plan, or so-called "poison pill," that would work to dilute the stock ownership of a potential hostile acquirer, effectively preventing acquisitions that have not been approved by our board of directors; and
- require the approval of the holders of at least $66^{2}/_{3}\%$ of the votes that all our stockholders would be entitled to cast to amend or repeal certain provisions of our charter or bylaws.

Moreover, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the Delaware General Corporation Law, or DGCL, which prohibits a person who owns in excess of 15% of our outstanding voting stock from merging or combining with us for a period of three years after the date of the transaction in which the person acquired in excess of 15% of our outstanding voting stock, unless the merger or combination is approved in a prescribed manner. These provisions could discourage potential acquisition proposals and could delay or prevent a change in control transaction. They could also have the effect of discouraging others from making tender offers for our common stock, including transactions that may be in your best interests. These provisions may also prevent changes in our management or limit the price that investors are willing to pay for our stock.

Our governing documents designate certain courts as the sole and exclusive forum for certain types of actions and proceedings that may be initiated by our stockholders, which could limit our stockholders' ability to obtain a favorable judicial forum for disputes with us or our directors, officers or employees.

Our amended and restated certificate of incorporation provides that, with respect to any state actions or proceedings under Delaware statutory or common 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 or any of our directors, officers, employees or agents arising under the DGCL, our amended and restated certificate of incorporation or our amended and restated bylaws;
- any action or proceeding to interpret, apply, enforce or determine the validity of our amended and restated certificate of incorporation or our amended and restated bylaws; and
- any action asserting a claim against us or any of our directors, officers, employees or agents that is governed by the internal-affairs doctrine.

In addition, our amended and restated bylaws provide that, unless we consent in writing to the selection of an alternative forum, the federal district courts of the United States are, to the fullest extent permitted by law, the exclusive forum for the resolution of any complaint asserting a cause of action arising under the Securities Act.

These exclusive-forum provisions may limit a stockholder's ability to bring a claim in a judicial forum that it finds favorable for disputes with us or our directors, officers or other employees, which may discourage lawsuits against us and our directors, officers and other employees. If a court were to find an exclusive-forum provision in our amended and restated certificate of incorporation or our amended and restated bylaws to be inapplicable or unenforceable in an action, we may incur additional costs associated with resolving the dispute in other jurisdictions, which could harm our business.

ITEM 1B. UNRESOLVED STAFF COMMENTS.

None.

ITEM 2. PROPERTIES.

Our corporate headquarters are located at 545 Fifth Ave, Suite 1400, New York, NY 10017 where we lease office space pursuant to a lease agreement that commenced on October 31, 2019 and expires on October 31, 2024. We also occupy space for offices in Englewood Cliffs, New Jersey pursuant to a lease which commenced on November 1, 2020 for a three year period. We believe that our existing facilities are suitable and adequate to meet our current needs. We intend to add new facilities or expand existing facilities as we add employees, and we believe that suitable additional or substitute space will be available as needed to accommodate any such expansion of our operations.

ITEM 3. LEGAL PROCEEDINGS.

We are not a party to any material legal proceedings, and we are not aware of any material claims or actions pending or threatened against us. In the future, we might from time to time become involved in litigation relating to claims arising from our ordinary course of business, the resolution of which we do not anticipate would have a material adverse impact on our financial position, results of operations or cash flows.

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

On May 16, 2019, our common stock began trading on the Nasdaq Global Market under the symbol "APLT." Prior to that time, there was no public market for our common stock.

Stockholders

As of December 31, 2022, there were approximately 20 stockholders of record of our common stock. The actual number of holders of our common stock is greater than this number of record holders, and includes stockholders who are beneficial owners, but whose shares are held in street names by brokers or held by 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 paid or declared any cash dividends on our common stock, and we do not anticipate paying any cash dividends on our common stock in the foreseeable future. We intend to retain all available funds and any future earnings to fund the development and expansion of our business. Any future determination to pay dividends will be at the discretion of our board of directors and will depend upon a number of factors, including our results of operations, financial condition, future prospects, contractual restrictions, restrictions imposed by applicable law and other factors that our board of directors deems relevant.

Recent Sales of Unregistered Securities

None.

Issuer Purchases of Equity Securities

We did not purchase any of our registered equity securities during the period covered by this Annual Report.

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 financial statements and the related notes included elsewhere in this Annual Report. Some of the information contained in this discussion and analysis or set forth elsewhere in this Annual Report, including information with respect to our plans and strategy for our business and related financing, includes forward-looking statements that involve risks and uncertainties. As a result of many factors, including those factors set forth in the "Risk Factors" section of this Annual Report, our actual results could differ materially from the results described in or implied by these forward-looking statements.

Overview

We are a clinical-stage biopharmaceutical company developing a pipeline of novel product candidates against validated molecular targets in indications of high unmet medical need. We focus on molecules and pathways whose role in the disease process is well known based on prior research, but have previously failed to yield successful products due to poor efficacy and tolerability. Our unique approach to drug development leverages recent technological advances to design improved drugs, employs early use of biomarkers to confirm biological activity and focuses on abbreviated regulatory pathways. Our first molecular target is aldose reductase, or AR, an enzyme that converts glucose to sorbitol under oxidative stress conditions, and is implicated in multiple diseases. Prior attempts to inhibit this enzyme were hindered by nonselective, nonspecific inhibition, which resulted in limited efficacy and significant off-target safety effects. The detrimental consequences of AR activation have been well established by decades of prior research. Our AR program currently includes three small molecules, which are all potent and selective inhibitors of AR, but are engineered to have unique tissue permeability profiles to target different disease states, including diabetic complications, heart disease and rare metabolic diseases. The result of this unique multifaceted approach to drug development is a portfolio of highly specific and selective product candidates that we believe are significantly de-risked and can move quickly through the development process.

AT-007 is a novel central nervous system, or CNS, penetrant ARI that we are developing for the treatment of rare metabolic diseases, including Galactosemia and SORD Deficiency. Galactosemia is a devastating rare pediatric metabolic disease that affects how the body processes a simple sugar called galactose, and for which there is no known cure or approved treatment available. The U.S. Food and Drug Administration, or FDA, has granted both orphan drug designation and rare pediatric disease designation to AT-007 for the treatment of Galactosemia and in June 2021, the FDA granted Fast Track Designation to AT-007 for the treatment of Galactosemia. We have completed an adult study in healthy volunteers and Galactosemia patients, demonstrating that AT-007 is safe and well tolerated, and significantly reduces plasma galactitol levels vs. placebo. Galactitol is a toxic metabolite of galactose, which is formed in Galactosemia patients by aberrant activity of aldose reductase when galactose is present at high levels. A pediatric study is underway in children with Galactosemia, assessing the impact of AT-007 vs. placebo on safety, biomarker reduction of galactitol, and long-term functional outcomes. On April 13, 2021, we presented data featuring a cross-sectional analysis of nineteen pediatric patients with Classic Galactosemia, providing meaningful insight on the progressive worsening of the central nervous system phenotype with age. On October 18, 2021, we reported biomarker data from the pediatric ACTION-Galactosemia Kids study. The results demonstrate a substantial reduction in plasma galactitol of approximately 40%, which was statistically significant ($p<0.001$) vs. placebo. We previously reported a baseline analysis of the 47 children enrolled in the study which demonstrated a clear correlation between baseline galactitol levels and baseline clinical functional outcomes. The long-term functional outcomes portion of the pediatric study is ongoing, and the outcomes are assessed every 6 months by a fire-walled data monitoring committee (DMC). When the study reaches statistical significance in the active treated arm vs. the placebo arm, the DMC will alert the Company and the trial will be unblinded. In April 2022, the Company met with the FDA to discuss the design of the ongoing pediatric study prior to the first 6-month outcomes assessment by the DMC. The FDA confirmed that the pediatric study as it is currently designed would support an NDA submission if statistical significance is reached, and there is alignment between the FDA and the Company on the potential path forward to approval. The 12-month clinical outcomes were assessed by the

fire-walled DMC, and as expected the data did not yet reach statistical significance, but demonstrated a trend in clinical outcomes favoring AT-007 vs. placebo. A safety analysis showed that AT-007 continued to be safe and well tolerated. The Company is exploring a potential submission for conditional approval based on existing data with the European Medicines Agency (EMA).

AT-007 is also being studied in a rare disease caused by deficiency in the enzyme Sorbitol Dehydrogenase. Aldose Reductase is the first enzyme in the polyol pathway, converting glucose to sorbitol. AR is then followed by Sorbitol Dehydrogenase, which converts sorbitol to fructose. Patients with SORD Deficiency accumulate very high levels of sorbitol in their cells and tissues as a result of the enzyme deficiency, which results in tissue toxicities such as peripheral neuropathy and motor neuron disease. Recent research in drosophila and cell models of SORD Deficiency demonstrated that treatment with an ARI that blocks sorbitol production may provide benefit in this disease. Preclinical studies on AT-007 have demonstrated significant reduction in sorbitol levels in fibroblasts from SORD deficient patients. Treatment with AT-007 in the drosophila model of SORD prevented the disease phenotype and protected from neuronal degeneration. On October 25, 2021, we reported data from a pilot open-label study in 8 SORD Deficiency patients. AT-007 reduced blood sorbitol levels by approximately 66% from baseline through 30 days of treatment. AT-007 was safe and well tolerated in all treated patients. In December 2021, we initiated a Phase 2/3 registrational study in patients with SORD Deficiency, which is ongoing at multiple clinical sites in the US and Europe. On February 16, 2023, we announced that in a pre-specified interim analysis of the ongoing Phase 3 INSPIRE trial, AT-007 reduced sorbitol levels by a mean of approximately 52% (or approximately 16,000ng/ml) over 90 days of treatment ($p<0.001$ vs. placebo) in patients with SORD Deficiency. At baseline, the mean blood sorbitol level of SORD patients included in this interim analysis was approximately 29,000ng/ml, with a range of approximately 22,000ng/ml-38,000ng/ml. In the INSPIRE trial, a baseline cross-sectional analysis of the relationship between sorbitol level, age (or duration of disease) and clinical outcome measures demonstrated a statistically significant correlation between sorbitol level and key clinical outcome measures, including 10-meter-walk/run speed, 4-stair climb speed, and sit-to-stand test ($p<0.05$). The Company is working with the FDA to determine the appropriate regulatory path forward, as well as data required for an NDA submission, to advance AT-007 towards registration for this indication. The INSPIRE study will continue in blinded format to the 12-month interim clinical outcomes assessment. If the primary clinical outcome measure (10-meter-walk/run) reaches statistical significance at 12 months, the study will be completed and unblinded. If not, the study will continue in blinded format to 24 months, where clinical outcomes will be assessed again in a final statistical analysis. AT-007 continues to be safe and well tolerated to date.

We also plan to initiate a clinical development program on AT-007 in another pediatric rare disease, called PMM2-CDG. PMM2-CDG is a glycosylation disorder caused by deficiencies in the enzyme phosphomannomutase 2, which leads to CNS symptoms similar to Galactosemia, including low IQ, tremor, and speech and motor problems. Aldose Reductase is over-activated in this disease as a compensatory consequence of PMM2 deficiency, and a CNS penetrant ARI may be a compelling clinical option. Initial data in fibroblast cell lines derived from PMM2-CDG patients demonstrates that AT-007 treatment increases phosphomannomutase 2 activity. The FDA has granted pediatric rare disease designation and orphan designation for AT-007 in PMM2-CDG.

AT-001 is a novel ARI with broad systemic exposure and peripheral nerve permeability that we are developing for the treatment of diabetic cardiomyopathy, or DbCM, a fatal fibrosis of the heart, for which no treatments are available. We completed a Phase 1/2 clinical trial evaluating AT-001 in approximately 120 patients with type 2 diabetes, in which no drug-related adverse effects or tolerability issues were observed. In September 2019, we announced the initiation of a Phase 3 registrational trial of AT-001 in DbCM. The study, called ARISE-HF, is designed to evaluate AT-001's ability to improve or prevent the decline of functional capacity in patients with DbCM at high risk of progression to overt heart failure. Although we did experience enrollment delays in 2020 associated with the Covid-19 pandemic, modifications were made to the trial to include additional sites and geographies to address Covid-19-related issues. The trial is now fully enrolled with 675 patients.

AT-003 is a novel ARI designed to cross through the back of the eye when dosed orally, and has demonstrated strong retinal penetrance, for the treatment of diabetic retinopathy, or DR. DR is an ophthalmic disease that occurs in diabetic patients and for which treatments are currently limited to high-cost biologics requiring intravitreal administration. DR has been linked to AR activity, including elevations in sorbitol and subsequent changes in retinal blood vessels, which distorts vision and leads to permanent blindness.

AT-104 is a preclinical dual selective PI3K inhibitor. Due to recent regulatory changes impacting development of the PI3K inhibitor class of compounds, the Company has discontinued its early stage preclinical PI3K program and further development of AT-104. The compound and all rights associated with the technology were returned to Columbia University.

Since inception in 2016, our operations have focused on developing our product candidates, organizing and staffing our company, business planning, raising capital, establishing our intellectual property portfolio and conducting clinical trials. We do not have any product candidates approved for sale and have not generated any revenue.

We have incurred significant operating losses since inception in 2016. Our ability to generate product revenue sufficient to achieve profitability will depend on the successful development and commercialization of one or more of our product candidates. Our net loss was $82.5 million for the year ended December 31, 2022. As of December 31, 2022, we had an accumulated deficit of $348.8 million. We expect to continue to incur significant expenses and increasing operating losses for the foreseeable future in connection with our ongoing activities. Furthermore, we expect to incur additional costs associated with operating as a public company, including significant legal, accounting, investor relations and other expenses. As of December 31, 2022, we had cash and cash equivalents and short-term investments of $30.6 million.

February 2021 Secondary Public Offering

In February 2021, we issued and sold 3,000,000 shares of common stock at a public offering price of $23.00 per share, with an additional 450,000 shares sold pursuant to the underwriters' full exercise of their option to purchase additional shares in the February Offering. We received aggregate proceeds, net of underwriting discounts and commissions and offering costs of $74.4 million.

June 2022 Offering

On June 27, 2022, the Company completed the June Offering, an underwritten public offering of 20,000,000 shares of common stock, par value $0.0001 per share, 10,000,000 Pre-Funded Warrants, and accompanying Common Warrants to purchase up to 30,000,000 shares of common stock. The shares and accompanying Common Warrants were offered at a price to the public of $1.00 per share and warrant, and the Pre-Funded Warrants and accompanying Common Warrants were offered at a price to the public of $0.9999, resulting in aggregate net proceeds of approximately $27.8 million, after deducting underwriting discounts and commissions and offering expenses. The Pre-Funded Warrants and the Common Warrants are immediately exercisable and will expire five years from the date of issuance. Holders may not exercise any Pre-Funded Warrants or Common Warrants that would cause the aggregate number of shares of common stock beneficially owned by the holder to exceed 9.99% of the Company's outstanding common stock immediately after exercise. Holders of the Pre-Funded Warrants and/or Common Warrants (together with affiliates) who immediately prior to June 27, 2022 beneficially owned more than 9.99% of the Company's outstanding common stock may not exercise any portion of their Pre-Funded Warrants or Common Warrants if the holder (together with affiliates) would beneficially own more than 19.99% of the Company's outstanding common stock after exercise. The Pre-Funded Warrants and Common Warrants are subject to adjustment in the event of certain stock dividends and distributions, stock splits, stock combinations, reclassifications or similar events affecting the common stock and also upon any distributions for no consideration of assets to the Company's stockholders. In the event of certain corporate transactions, the holders of the Pre-Funded Warrants and/or Common Warrants will be entitled to receive, upon exercise, the kind and amount of securities, cash or other property that the holders would have received had they exercised the Pre-Funded Warrants and/or Common Warrants immediately prior to such transaction. The Pre-Funded Warrants and Common Warrants do not entitle the holders thereof to any voting rights or any of the other rights or privileges to which the Company's stockholders are entitled. The Company intends to use the net proceeds from the June Offering for general corporate purposes, which may include research and development costs, including the conduct of clinical trials and process development and manufacturing of the Company's product candidates, expansion of the Company's research and development capabilities, working capital and capital expenditures.

Components of Our Results of Operations

Revenue

Since inception, we have not generated any revenue and do not expect to generate any revenue from the sale of products in the near future. If our development efforts for our product candidates are successful and result in regulatory approval, or if we enter into collaboration or license agreements with third parties, we may generate revenue in the future from a combination of product sales or payments from collaboration or license agreements.

Operating Expenses

Research and Development Expenses

Research and development expenses consist primarily of costs incurred for our research activities, including our discovery efforts and the development of our product candidates, and include:

- employee-related expenses, including salaries, related benefits and stock-based compensation expense for employees engaged in research and development functions;
- fees paid to consultants for services directly related to our product development and regulatory efforts;
- expenses incurred under agreements with contract research organizations, or CROs, as well as contract manufacturing organizations, or CMOs, and consultants that conduct and provide supplies for our preclinical studies and clinical trials;
- costs associated with preclinical activities and development activities;
- costs associated with our technology and our intellectual property portfolio; and
- costs related to compliance with regulatory requirements.

We expense research and development costs as incurred. Costs for external development activities are recognized based on an evaluation of the progress to completion of specific tasks using information provided to us by our vendors. Payments for these activities are based on the terms of the individual agreements, which may differ from the pattern of costs incurred, and are reflected in our financial statements as prepaid or accrued research and development expenses.

Research and development costs also include costs incurred in connection with certain licensing arrangements. Before a compound receives regulatory approval, we record upfront and milestone payments made by us to third parties under licensing arrangements as expense. Upfront payments are recorded when incurred, and milestone payments are recorded when the specific milestone has been achieved. Once a compound receives regulatory approval, we will record any milestone payments in Identifiable intangible assets, less accumulated amortization and, unless the asset is determined to have an indefinite life, we will amortize the payments on a straight-line basis over the remaining agreement term or the expected product life cycle, whichever is shorter.

Research and development activities are central to our business model. We expect that our research and development expenses will continue to increase for the foreseeable future as we continue clinical development for our product candidates and continue to discover and develop additional product candidates. If any of our product candidates enter into later stages of clinical development, they will generally have higher development costs than those in earlier stages of clinical development, primarily due to the increased size and duration of later-stage clinical trials. Historically, we have incurred research and development expenses that primarily relate to the development of AT-007, AT-001 and our ARI program. As we advance our product candidates, we expect to allocate our direct external research and development costs across each of the indications or product candidates.

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

(in thousands)	Year Ended December 31, 2022	2021
Product pipeline research and development expenses		
AT-001	$ 20,809	$ 22,861
AT-007	23,902	30,669
Personnel-related expenses	6,648	5,529
Stock-based compensation	3,618	2,759
Other expenses	657	752
Total research and development expenses	$ 55,634	$ 62,570

General and Administrative Expenses

General and administrative expenses consist primarily of salaries and other related costs, including stock-based compensation, for personnel in our executive, finance, and commercial functions. General and administrative expenses also include professional fees for legal, accounting, auditing, tax and consulting services; travel expenses; and facility-related expenses, which include allocated expenses for rent and maintenance of facilities and other operating costs.

Commercial expenses consist of payroll expense for commercial personnel, as well as marketing, market research, market access, and other focused investments to support launch of drug candidates, generate evidence of commercial potential and value proposition, and maximize potential business development deal leverage. Commercial expenses are included in general and administrative expenses.

We expect that our general and administrative expenses will increase in the future as we increase our general and administrative headcount to support our continued research and development and potential commercialization of our product candidates. We also expect to incur increased expenses associated with being a public company, including costs of accounting, audit, legal, regulatory and tax compliance services; director and officer insurance costs; and investor and public relations costs.

Other Income (Expense), Net

Other income (expense), net consists of interest income (expense), net, and other income (expense), net. Interest income (expense), net consists primarily of our interest income on our cash and cash equivalents and marketable securities. Other income (expense), net consists primarily of realized gains and losses on sales of marketable securities.

Results of Operations

The following table summarizes our results of operations:

	Years Ended December 31,	
(in thousands)	**2022**	**2021**
Operating expenses:		
Research and development	$ 55,634	$ 62,570
General and administrative	27,316	43,048
Total operating expenses	82,950	105,618
Loss from operations	(82,950)	(105,618)
Other income (expense), net:		
Interest income (expense), net	685	555
Change in fair value of warrant liabilities	(66)	—
Other income (expense)	(177)	(521)
Other income (expense), net	442	34
Net loss	$ (82,508)	$ (105,584)

Research and Development Expenses

The following table summarizes our research and development expenses:

	Year Ended December 31,		
(in thousands)	**2022**	**2021**	**Increase / (Decrease)**
Clinical and pre-clinical	$ 42,928	$ 40,323	$ 2,605
Drug manufacturing and formulation	957	11,910	(10,953)
Personnel expenses	6,648	5,529	1,119
Stock-based compensation	3,619	2,759	860
Regulatory and other	1,482	2,049	(567)
Total research and development expenses	$ 55,634	$ 62,570	$ (6,936)

Research and development expenses for the year ended December 31, 2022 were $55.6 million, compared to $62.6 million for the year ended December 31, 2021. The decrease of approximately $6.9 million was primarily related to:

- an increase in clinical and pre-clinical expense of $2.6 million, primarily related to the progression of the SORD Phase 2/3 registrational study, progression of the AT-007 ACTION-Galactosemia long-term extension adult study, and progression of the AT-007 ACTION-Galactosemia Kids pediatric registrational study;
- a decrease in drug manufacturing and formulation expenses of $11.0 million primarily related to the completion and release of AT-001 and AT-007 drug product batches in the year ended December 31, 2021;
- an increase in personnel expenses of $1.1 million due to the increase in headcount in support of our clinical program pipeline;
- an increase in stock-based compensation of $0.9 million due to new stock option and restricted stock unit grants, offset by forfeitures of stock option and restricted stock unit grants;

- a decrease of regulatory and other expenses of $0.6 million primarily related to the UM license fees recognized during the year ended December 31, 2021.

General and Administrative Expenses

The following table summarizes our general and administrative expenses:

(in thousands)	Year Ended December 31, 2022	2021	Increase / (Decrease)
Legal and professional fees	$ 6,854	$ 6,340	$ 514
Commercial expenses	2,193	11,341	(9,148)
Personnel expenses	5,537	6,617	(1,080)
Stock-based compensation	5,543	8,418	(2,875)
Insurance expenses	3,682	4,399	(717)
Other expenses	3,507	5,933	(2,426)
Total general and administrative expenses	$ 27,316	$ 43,048	$ (15,732)

General and administrative expenses were $27.3 million for the year ended December 31, 2022, compared to $43.0 million for the year ended December 31, 2021. The decrease of approximately $15.7 million was primarily related to:

- an increase in professional and legal fees of $0.5 million due to higher external legal fees;
- a decrease of $9.1 million related to decreased spend for commercial operations;
- a decrease in personnel expenses of $1.1 million and a decrease in stock-based compensation of $2.9 million due to a decrease in headcount;
- a decrease of insurance expenses of $0.7 million related to decreased directors and officers liability insurance costs; and
- a decrease in other expenses of $2.4 million, primarily relating to decreased costs of other office expenses.

Other Income (Expense), Net

Interest income was $0.7 million for the year ended December 31, 2022 as compared to $0.6 million for the year ended December 31, 2021. Interest income is derived from our marketable securities and the increase of $0.1 million in interest income year over year is due to rising interest rates during 2022.

Change in fair value of warrant liabilities - The change in the fair value of our warrant liabilities for the year ended December 31, 2022 resulted in a $0.1 million expense recognized in the period. There were no warrant liabilities for the year ended December 31, 2021.

Other expense, net was expense of approximately $0.2 million for the year ended December 31, 2022, compared to expense of $0.5 million for the year ended December 31, 2021. The decrease was primarily related to lower realized losses incurred by our available-for-sale securities portfolio during the year ended December 31, 2022.

Liquidity and Capital Resources

Since our inception through December 31, 2022, we have not generated any revenue and have incurred significant operating losses and negative cash flows from our operations. The accompanying financial statements have

been prepared assuming the continuation of the Company as a going concern. The exclusive licensing agreement with Advanz Pharma for commercialization rights to AT-007 in Europe is expected to provide a source of capital to the Company based on clinical and regulatory milestones. If actualization of these milestones aligns with the projected timelines, and product approvals are received in the timeframes expected, this source of capital may be sufficient to cover operating expenses through expected product approvals and potential revenues. However, there are no guarantees that this will materialize, and delays or unexpected data could disrupt this potential source of liquidity. Broadly, the Company has not yet established an ongoing source of revenues sufficient to cover its operating costs and is dependent on debt and equity financing to fund its operations. As of December 31, 2022, our cash, cash equivalents and marketable securities was $30.6 million. We also received a $10.7 million upfront payment from Advanz Pharma in January 2023 in conjunction with signing the exclusive licensing agreement for European commercialization rights. We believe that our cash and cash equivalents as of December 31, 2022, along with the upfront payment received in January 2023 and the projected clinical and regulatory milestone payments expected in fiscal year 2023 from Advanz Pharma will be sufficient to fund our operations through year end 2023, and potentially beyond if clinical trial completion and marketing authorization in Europe as well as commercial sales milestones materialize in the expected timelines. The report of our independent registered public accounting firm on our financial statements for the year ended December 31, 2022 includes an explanatory paragraph regarding the existence of substantial doubt about our ability to continue as a going concern. Given our planned expenditures for the next several years, we have concluded and our independent registered public accounting firm has agreed with our conclusion that there is still a substantial doubt regarding our ability to continue as a going concern for a period of 12 months beyond the filing of this Form 10-K.

Cash Flows

The following table summarizes our cash flows for each of the periods presented:

	Year Ended December 31,	
(in thousands)	**2022**	**2021**
Net cash used in operating activities	$ (78,093)	$ (90,728)
Net cash provided by/(used in) investing activities	13,170	12,433
Net cash provided by financing activities	27,692	74,717
Net increase (decrease) in cash and cash equivalents	$ (37,231)	$ (3,578)

Operating Activities

During the year ended December 31, 2022, operating activities used cash of $78.1 million, due to our net losses of $82.6 million, a decrease in operating lease liability of $0.4 million, a decrease in financed insurance premium of $3.1 million, a decrease of $1.6 million in accrued expense, and a decrease in accounts payable of $4.9 million. This is partially offset by increases of $0.4 million in prepaid expense, $0.4 million of issuance of options in-lieu of bonus, $9.2 million in non-cash stock-based compensation expense, and $3.6 million of amortization of insurance premium, an increase of $0.1 million in change in fair value of warrant liability, and $0.4 million in amortization of operating lease right-of-use assets.

During the year ended December 31, 2021, operating activities used cash of $90.7 million, due to our net losses of $105.6 million, a decrease in operating lease liability of $0.4 million, a decrease in financed insurance premium of $4.4 million, a decrease of $3.3 million in accrued expense, and a decrease in prepaid expenses of $1.7 million. This is partially offset by increases of $8.8 million in accounts payable, $11.2 million in non-cash stock-based compensation expense, and $4.3 million of amortization of insurance premium, and $0.4 million in amortization of operating lease right-of-use assets.

Investing Activities

Net cash provided by investing activities for the year ended December 31, 2022 was $13.2 million relating to our purchases of available-for-sale marketable securities for $64.2 million and proceeds from the maturities of available-for-sale marketable securities for $77.4 million.

Net cash provided by investing activities for the year ended December 31, 2021 was $12.4 million relating to our purchases of available-for-sale marketable securities for $121.6 million and proceeds from the sale and maturities of available-for-sale marketable securities for $134.0 million.

Financing Activities

During the year ended December 31, 2022, net cash provided by financing activities was $27.7 million, primarily from the cash proceeds from the June 2022 offering of $27.8 million, $49,000 from the exercise of stock options for common stock under the 2019 Plan, and $3.1 million from the proceeds from financed insurance premium. This was partially offset by the repayment of short-term borrowings of $3.3 million.

In June 2020, we entered into the Goldman Equity Distribution Agreement to sell shares of our common stock, from time to time, having an aggregate offering price of up to $100 million. The Goldman Equity Distribution Agreement was terminated as of January 24, 2022.

On January 26, 2022, the Company entered into the Cowen Equity Distribution Agreement to sell shares of the Company's common stock, from time to time, having an aggregate offering price of up to $100.0 million. Pursuant to the Cowen Equity Distribution Agreement shares of our common stock may be offered and sold through the sales agent in sales deemed "at-the-market" offerings under the Securities Act of 1933, as amended, or the Securities Act. Under the Cowen Equity Distribution Agreement, the sales agent will be entitled to compensation of up to 3% of the gross offering proceeds of all shares of our common stock sold through it pursuant to the Cowen Equity Distribution Agreement. In connection with the sale of shares of our common stock on our behalf, the sales agent may be deemed to be "underwriters" within the meaning of the Securities Act, and the compensation paid to the sales agent may be deemed to be underwriting commissions or discounts. As of December 31, 2022, the Company has not sold any shares of common stock pursuant to the Cowen Equity Distribution Agreement.

On June 27, 2022, the Company completed the June Offering, an underwritten public offering of 20,000,000 shares of common stock, par value $0.0001 per share, 10,000,000 Pre-Funded Warrants, and accompanying Common Warrants to purchase up to 30,000,000 shares of common stock. The shares and accompanying Common Warrants were offered at a price to the public of $1.00 per share and warrant, and the Pre-Funded Warrants and accompanying Common Warrants were offered at a price to the public of $0.9999, resulting in aggregate net proceeds of approximately $27.8 million, after deducting underwriting discounts and commissions and offering expenses. The Pre-Funded Warrants and the Common Warrants are immediately exercisable and will expire five years from the date of issuance. Holders may not exercise any Pre-Funded Warrants or Common Warrants that would cause the aggregate number of shares of common stock beneficially owned by the holder to exceed 9.99% of the Company's outstanding common stock immediately after exercise. Holders of the Pre-Funded Warrants and/or Common Warrants (together with affiliates) who immediately prior to June 27, 2022 beneficially owned more than 9.99% of the Company's outstanding common stock may not exercise any portion of their Pre-Funded Warrants or Common Warrants if the holder (together with affiliates) would beneficially own more than 19.99% of the Company's outstanding common stock after exercise. The Pre-Funded Warrants and Common Warrants are subject to adjustment in the event of certain stock dividends and distributions, stock splits, stock combinations, reclassifications or similar events affecting the common stock and also upon any distributions for no consideration of assets to the Company's stockholders. In the event of certain corporate transactions, the holders of the Pre-Funded Warrants and/or Common Warrants will be entitled to receive, upon exercise, the kind and amount of securities, cash or other property that the holders would have received had they exercised the Pre-Funded Warrants and/or Common Warrants immediately prior to such transaction. The Pre-Funded Warrants and Common Warrants do not entitle the holders thereof to any voting rights or any of the other rights or privileges to which the Company's stockholders are entitled. The Company intends to use the net proceeds from the June Offering for general corporate purposes, which may include research and development costs, including the conduct of clinical trials and process development and manufacturing of the Company's product candidates, expansion of the Company's research and development capabilities, working capital and capital expenditures.

During the year ended December 31, 2021, net cash provided by financing activities was $74.7 million, primarily from the cash proceeds from the secondary offering of $74.4 million, $0.5 million from the exercise of stock options for common stock under the 2019 Plan, and $69,000 from the exercise of warrants for common stock, and $4.4

million from the proceeds from financed insurance premium. This was partially offset by the repayment of short-term borrowings of $4.7 million.

Funding Requirements

We expect our expenses to increase substantially in connection with our ongoing activities, particularly as we advance the preclinical activities and clinical trials of our product candidates. We believe that our expenses may increase significantly if and as we:

- continue the ongoing and planned development of our product candidates;
- initiate, conduct and complete any ongoing, anticipated or future preclinical studies and clinical trials for our current and future product candidates;
- seek marketing approvals for any product candidates that successfully complete clinical trials;
- establish a sales, marketing, manufacturing and distribution infrastructure to commercialize any current or future product candidate for which we may obtain marketing approval;
- seek to discover and develop additional product candidates;
- continue to build a portfolio of product candidates through the acquisition or in-license of drugs, product candidates or technologies;
- maintain, protect and expand our intellectual property portfolio;
- hire additional clinical, regulatory and scientific personnel; and
- add operational, financial and management information systems and personnel, including personnel to support our product development and planned future commercialization efforts.

Furthermore, we have and expect to incur additional costs associated with operating as a public company, including significant legal, accounting, investor relations and other expenses.

Due to the numerous risks and uncertainties associated with the development of our product candidates and programs, and because the extent to which we may enter into collaborations with third parties for development of our product candidates is unknown, we are unable to estimate the timing and amounts of increased capital outlays and operating expenses associated with completing the research and development of our product candidates. Our future funding requirements, both near and long-term, will depend on many factors, including:

- the initiation, scope, progress, timing, costs and results of our ongoing and planned clinical trials for our product candidates;
- the outcome, timing and cost of meeting regulatory requirements established by the FDA and other comparable foreign regulatory authorities;
- the cost of filing, prosecuting, defending and enforcing our patent claims and other intellectual property rights;
- the cost of defending potential intellectual property disputes, including patent infringement actions;
- the achievement of milestones or occurrence of other developments that trigger payments under the Columbia Agreements or other agreements we may enter into;
- the extent to which we are obligated to reimburse, or entitled to reimbursement of, clinical trial costs under future collaboration agreements, if any;
- the effect of competing technological and market developments;
- the cost and timing of completion of clinical or commercial-scale manufacturing activities;
- the costs of operating as a public company;
- the extent to which we in-license or acquire other products and technologies;
- our ability to establish and maintain collaborations on favorable terms, if at all;
- the cost of establishing sales, marketing and distribution capabilities for our product candidates in regions where we choose to commercialize our product candidates, if approved; and
- the initiation, progress, timing and results of the commercialization our product candidates, if approved, for commercial sale.

A change in the outcome of any of these variables with respect to the development of a product candidate could mean a significant change in the costs and timing associated with the development of that product candidate.

Until such time, if ever, that we can generate product revenue sufficient to achieve profitability, we expect to finance our cash needs through offerings of securities, PIPE, debt financings, collaborations or other strategic transactions. The terms of financing may adversely affect the holdings or the rights of our stockholders. Funding may not be available to us on acceptable terms, or at all. If we are unable to obtain funding, we may be required to delay, limit, reduce or terminate some or all of our research and product development, product portfolio expansion or future commercialization efforts. If we raise additional capital through debt financing, we may be subject to covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends.

Contractual Obligations and Commitments

The following table summarizes our contractual obligations as of December 31, 2022:

	Payments Due By Period				
(in thousands)	Total	Less Than 1 Year	1 to 3 Years	4 to 5 Years	More Than 5 Years
Operating lease commitments[1]	$ 940	$ 515	$ 425	$ —	$ —
Total	$ 940	$ 515	$ 425	$ —	$ —

(1) Represents future minimum lease payments under our operating leases for office space.

Except as disclosed in the table above, we have no long-term debt or capital leases and no material non-cancelable purchase commitments with service providers, as we have generally contracted on a cancelable, purchase-order basis. We enter into contracts in the normal course of business with CROs, CMOs and other third parties for clinical trials, preclinical research studies and testing and manufacturing services. These contracts are cancelable by us upon prior notice. Payments due upon cancellation consist only of payments for services provided or expenses incurred, including noncancelable obligations of our service providers, up to the date of cancellation. These payments are not included in the preceding table as the amount and timing of such payments are not known.

We may incur potential contingent payments upon our achievement of clinical, regulatory and commercial milestones, as applicable, or royalty payments that we may be required to make under the 2016 and 2019 Columbia Agreements, the 2020 Miami License Agreement, the 2020 Miami Option Agreement, and the 2020 Miami Research Agreement, pursuant to which we have in-licensed certain intellectual property. Due to the uncertainty of the achievement and timing of the events requiring payment under these agreements, the amounts to be paid by us are not fixed or determinable at this time and are excluded from the table above. See the section titled “Business—Exclusive License Agreement with Columbia University” and “Business—License Agreement with University of Miami.”

Critical Accounting Policies and Significant Judgments and Estimates

Our management’s discussion and analysis of financial condition and results of operations is based on our financial statements, which have been prepared in accordance with U.S. generally accepted accounting principles, or U.S. GAAP. The preparation of our financial statements and related disclosures requires us to make estimates and assumptions that affect the reported amounts of assets and liabilities, costs and expenses and the disclosure of contingent assets and liabilities in our financial statements. 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 greater detail in Note 1 to our financial statements appearing elsewhere in 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 financial statements.

Accrued Research and Development Expenses

We expense all costs incurred in performing research and development activities. Research and development expenses include materials and supplies, preclinical expenses, manufacturing expenses, contract services and other outside expenses. As part of the process of preparing our financial statements, we are required to estimate our accrued research and development expenses. We make estimates of our accrued expenses as of each balance sheet date in the financial statements based on facts and circumstances known to us at that time. There may be instances in which payments made to our vendors will exceed the level of services provided and result in a prepayment of the expense. In accruing service fees, we estimate the time period over which services will be performed and the level of effort to be expended in each period. If the actual timing of the performance of services or the level of effort varies from the estimate, we adjust the accrual or the amount of prepaid expenses accordingly. Although we do not expect our estimates to be materially different from amounts actually incurred, our understanding of the status and timing of services performed relative to the actual status and timing of services performed may vary and may result in reporting amounts that are too high or too low in any particular period. To date, there have not been any material adjustments to our prior estimates of accrued research and development expenses. Nonrefundable advance payments for goods or services to be received in the future for use in research and development activities are deferred and capitalized. The capitalized amounts are expensed as the related goods are delivered or the services are performed.

Research and development costs also include costs incurred in connection with certain licensing arrangements. Before a compound receives regulatory approval, we record upfront and milestone payments made by us to third parties under licensing arrangements as expense. Upfront payments are recorded when incurred, and milestone payments are recorded when the specific milestone has been achieved. Once a compound receives regulatory approval, we will record any milestone payments in Identifiable intangible assets, less accumulated amortization and, unless the asset is determined to have an indefinite life, we will amortize the payments on a straight-line basis over the remaining agreement term or the expected product life cycle, whichever is shorter.

Stock-Based Compensation

We account for our stock-based compensation as expense in the statements of operations based on the awards' grant date fair values. We account for forfeitures as they occur by reversing any expense recognized for unvested awards.

We estimate the fair value of options granted using the Black-Scholes option pricing model. The Black-Scholes option pricing model requires inputs based on certain subjective assumptions, including (a) the expected stock price volatility, (b) the calculation of expected term of the award, (c) the risk-free interest rate and (d) expected dividends. Due to a historical lack of a public market for our common stock and a lack of company-specific historical and implied volatility data, we have based our estimate of expected volatility on the historical volatility of a group of similar companies that are publicly traded. The historical volatility is calculated based on a period of time commensurate with the expected term assumption. The computation of expected volatility is based on the historical volatility of a representative group of companies with similar characteristics to us, including stage of product development and life science industry focus. We use the simplified method as allowed by the SEC Staff Accounting Bulletin No. 107, Share-Based Payment, to calculate the expected term for options granted as we do not have sufficient historical exercise data to provide a reasonable basis upon which to estimate the expected term. The risk-free interest rate is based on a treasury instrument whose term is consistent with the expected term of the stock options. The expected dividend yield is assumed to be zero as we have never paid dividends and have no current plans to pay any dividends on our common stock. The fair value of stock-based payments is recognized as expense over the requisite service period which is generally the vesting period.

Warrant Liabilities

We account for our Warrant liabilities by measuring the fair value at inception and are then subsequently measured on a recurring basis, with changes in fair value recognized in other income (expense) within the Company's statement of operations.

We utilized a Black-Scholes option pricing model to estimate the fair value of the Common and Pre-Funded Warrants, which utilizes certain unobservable inputs and is therefore considered a Level 3 fair value measurement. Certain inputs used in this Black-Scholes pricing model may fluctuate in future periods based upon factors that are outside of the Company's control, including a potential change in control outside of the Company's control. A significant change in one or more of these inputs used in the calculation of the fair value may cause a significant change to the fair value of the Company's warrant liabilities, which could also result in material non-cash gains or losses being reported in the Company's consolidated statement of operations.

We utilized a probability-weighted approach that considered the probability of a change in control at the Company in the Black-Scholes option pricing model, whereby a 10% probability of change in control was used for each of the five years in the term of the agreements.

The inputs we utilized to value the warrant liability for Common and Pre-Funded Warrants are highly subjective. The assumptions used in calculating the fair value of the warrant liability for Common and Pre-Funded Warrants represent our best estimates, but these estimates involve inherent uncertainties and the application of management judgment. As a result, if factors change and we use different assumptions, the fair value of the warrant liability for Common Warrants may be materially different in the future.

Off-Balance Sheet Arrangements

We have not entered into any off-balance sheet arrangements and do not have any holdings in variable interest entities.

Recently Issued Accounting Pronouncements

A description of recently issued accounting pronouncements that may potentially impact our financial position and results of operations is disclosed in Note 1 to our financial statements appearing elsewhere in this Annual Report.

Emerging Growth Company Status

The Jumpstart Our Business Startups Act of 2012 permits an "emerging growth company" such as us to take advantage of an extended transition period to comply with new or revised accounting standards applicable to public companies until those standards would otherwise apply to private companies. We have irrevocably elected to "opt out" of this provision and, as a result, we will comply with new or revised accounting standards when they are required to be adopted by public companies that are not emerging growth companies.

ITEM 7A. QUANTITATIVE AND QUALITATIVE DISCLOSURES ABOUT MARKET RISK.

We are exposed to market risks in the ordinary course of our business. These risks primarily include interest rate sensitivities and foreign currency sensitivities.

Interest Rate Sensitivity

Our exposure to market risk relates to our cash, cash equivalents and investments of $30.6 million. The primary objective of our investment activities is to preserve principal while at the same time maximizing the income we receive without significantly increasing risk. Some of the financial instruments in which we invest could be subject to market risk where the interest rates may cause the value of the instruments to fluctuate. To minimize this risk, we intend to

maintain a portfolio which may include cash, cash equivalents and short-term investment securities available-for-sale in a variety of securities.

The securities in our investment portfolio are not leveraged and are classified as available-for-sale. These available-for-sale securities are short-term in nature and subject to minimal interest rate risk. All investments have a fixed interest rate and are carried at market value, which approximates cost. We do not use derivative financial instruments in our investment portfolio. A change of 50 to 100 basis points in interest rate would result in a change of $45,000 to $0.1 million, respectively, on the value of our investment portfolio.

We do not believe that our cash has significant risk of default or illiquidity. While we believe our cash and cash equivalents does not contain excessive risk, we cannot provide absolute assurance that in the future our investments will not be subject to adverse changes in market value. In addition, we maintain significant amounts of cash at one or more financial institutions that are in excess of federally insured limits. Inflation generally affects us by increasing our cost of labor and clinical trial costs. We do not believe that inflation has had a material effect on our results of operations during the periods presented.

As of December 31, 2022, we had $0.6 million of outstanding short-term debt relating to our financed directors' and officers' insurance premium. The interest rate on this short-term loan is fixed at 2.64% per annum, and when considering the remaining outstanding balance and the remaining term of the agreement ending in the second quarter of 2022, the loan is not subject to material interest rate risk.

Foreign Currency Sensitivity

Our primary operations are transacted in U.S. Dollars, however, certain service agreements with third parties are denominated in currencies other than the U.S. Dollar, primarily the Euro. As such, we are subject to foreign exchange risk and therefore, fluctuations in the value of the U.S. Dollar against the Euro may impact the amounts reported for expenses and obligations incurred under such agreements. We do not participate in any foreign currency hedging activities and we do not have any other derivative financial instruments. We did not recognize any significant exchange rate loss during the year ended December 31, 2022. A hypothetical 10% change in foreign exchange rates during any of the periods presented would not have a material impact on our financial condition or results of operations.

ITEM 8. FINANCIAL STATEMENTS AND SUPPLEMENTARY DATA.

The information required by this item is set forth in the financial statements filed with this report and are herein and incorporated by reference.

Report of Independent Registered Public Accounting Firm

The Shareholders and the Board of Directors of Applied Therapeutics, Inc.

Opinion on the Financial Statements

We have audited the accompanying balance sheets of Applied Therapeutics, Inc. (the Company) as of December 31, 2022 and 2021, the related statements of operations, comprehensive income (loss), stockholders' equity and cash flows for each of the two years in the period ended December 31, 2022, and the related notes (collectively referred to as the "financial statements"). In our opinion, the financial statements present fairly, in all material respects, the financial position of the Company at December 31, 2022 and 2021, and the results of its operations and its cash flows for each of the two years in the period ended December 31, 2022, in conformity with U.S. generally accepted accounting principles.

The Company's Ability to Continue as a Going Concern

The accompanying financial statements have been prepared assuming that the Company will continue as a going concern. As discussed in Note 1 to the financial statements, the Company has suffered recurring losses from operations, will require additional capital to fund operations, and has stated that substantial doubt exists about the Company's ability to continue as a going concern. Management's evaluation of the events and conditions and management's plans regarding these matters are also described in Note 1. The financial statements do not include any adjustments that might result from the outcome of this uncertainty.

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 2017.

New York, New York
March 23, 2023

Applied Therapeutics, Inc.

Balance Sheets

(in thousands except share and per share data)

	As of December 31, 2022	As of December 31, 2021
ASSETS		
CURRENT ASSETS:		
Cash and cash equivalents	$ 16,657	$ 53,888
Investments	13,923	26,935
Prepaid expenses and other current assets	6,728	7,571
Total current assets	37,308	88,394
Operating lease right-of-use asset	857	1,298
Security deposits and leasehold improvements	198	200
TOTAL ASSETS	$ 38,363	$ 89,892
LIABILITIES AND STOCKHOLDERS' EQUITY		
CURRENT LIABILITIES:		
Current portion of operating lease liabilities	$ 477	$ 442
Accounts payable	4,534	9,461
Accrued expenses and other current liabilities	14,756	16,559
Warrant liability	13,657	—
Total current liabilities	33,424	26,462
NONCURRENT LIABILITIES:		
Noncurrent portion of operating lease liabilities	414	891
Clinical holdback - long-term portion	464	—
Total noncurrent liabilities	878	891
Total liabilities	34,302	27,353
STOCKHOLDERS' EQUITY:		
Common stock, $0.0001 par value; 200,000,000 shares authorized as of December 31, 2022 and 100,000,000 shares authorized as of December 31, 2021; 48,063,358 shares issued and outstanding as of December 31, 2022 and 26,215,514 shares issued and outstanding as of December 31, 2021	5	3
Preferred stock, par value $0.0001; 10,000,000 shares authorized as of December 31, 2022 and December 31, 2021; 0 shares issued and outstanding as of December 31, 2022 and December 31, 2021	-	-
Additional paid-in capital	352,828	328,958
Accumulated other comprehensive gain/(loss)	51	(107)
Accumulated deficit	(348,823)	(266,315)
Total stockholders' equity	4,061	62,539
TOTAL LIABILITIES AND STOCKHOLDERS' EQUITY	$ 38,363	$ 89,892

The Notes to Financial Statements are an integral part of these statements.

Applied Therapeutics, Inc.

Statements of Operations

(in thousands except share and per share data)

	Year Ended December 31,	
	2022	2021
OPERATING EXPENSES:		
Research and development	$ 55,634	$ 62,570
General and administrative	27,316	43,048
Total operating expenses	82,950	105,618
LOSS FROM OPERATIONS	(82,950)	(105,618)
OTHER INCOME (EXPENSE), NET:		
Interest income	685	555
Change in fair value of warrant liabilities	(66)	—
Other expense	(177)	(521)
Total other income, net	442	34
Net loss	$ (82,508)	$ (105,584)
Net loss attributable to common stockholders—basic and diluted	$ (82,508)	$ (105,584)
Net loss per share attributable to common stockholders—basic and diluted	$ (2.18)	$ (4.12)
Weighted-average common stock outstanding—basic and diluted	37,825,431	25,598,181

The Notes to Financial Statements are an integral part of these statements.

Applied Therapeutics, Inc.

Statements of Comprehensive Income (Loss)

(in thousands)

	Year Ended December 31,	
	2022	**2021**
Net Loss	$ (82,508)	$ (105,584)
Other comprehensive income (loss)		
Unrealized gain (loss) on marketable securities	158	5
Other comprehensive gain (loss), net of tax	158	5
Comprehensive income (loss), net of tax	$ (82,350)	$ (105,579)

The Notes to Financial Statements are an integral part of these statements.

Applied Therapeutics, Inc.

Statements of Stockholders' Equity

(in thousands, except share and per share data)

	Common Stock $0.0001 Par Value		Additional Paid-in Capital	Accumulated Deficit	Accumulated Other Comprehensive Income (Loss)	Total Stockholders' Equity
	Shares	Amount				
BALANCE, January 1, 2021	22,493,661	$ 2	$ 242,780	$ (160,731)	$ (112)	$ 81,939
Issuance of common stock upon secondary public offering, net of issuance costs of $167	3,450,000	1	74,421	—	—	74,422
Exercise of options for common stock issued under Equity Incentive Plan	191,436	—	511	—	—	511
Restricted Stock Unit released for common stock issued under Equity Incentive Plan	52,562	—	—	—	—	—
Exercise of warrants for common stock	27,855	—	69	—	—	69
Stock-based compensation expense	—	—	11,177	—	—	11,177
Net loss	—	—	—	(105,584)	—	(105,584)
Other comprehensive income (loss)	—	—	—	—	5	5
BALANCE, December 31, 2021	26,215,514	3	328,958	(266,315)	(107)	62,539

	Common Stock $0.0001 Par Value		Additional Paid-in Capital	Accumulated Deficit	Accumulated Other Comprehensive Income (Loss)	Total Stockholders' Equity
	Shares	Amount				
BALANCE, January 1, 2022	26,215,514	$ 3	$ 328,958	$ (266,315)	$ (107)	$ 62,539
Issuance of common stock, pre-funded warrants, and common warrants sold for cash, net of issuance costs of $96	20,000,000	2	12,801	—	—	12,803
Exercise of pre-funded warrants for common stock	1,750,000	—	1,417	—	—	1,417
Exercise of options for common stock issued under Equity Incentive Plan	47,602	—	49	—	—	49
Restricted Stock Units released for common issued under Equity Incentive Plan	50,242	—	—	—	—	—
Stock-based compensation expense	—	—	9,162	—	—	9,162
Issuance of options in-lieu of bonus	—	—	441	—	—	441
Net loss	—	—	—	(82,508)	—	(82,508)
Other comprehensive income (loss)	—	—	—	—	158	158
BALANCE, December 31, 2022	48,063,358	$ 5	$ 352,828	$ (348,823)	$ 51	$ 4,061

The Notes to Financial Statements are an integral part of these statements.

Applied Therapeutics, Inc.

Statements of Cash Flows

(in thousands)

	Year Ended December 31,	
	2022	**2021**
OPERATING ACTIVITIES:		
Net loss	$ (82,508)	$ (105,584)
Adjustments to reconcile net loss to net cash used in operating activities:		
Stock-based compensation expense	9,162	11,177
Issuance of options in-lieu of bonus	441	—
Amortization of insurance premium	3,589	4,282
Amortization of operating lease right-of-use assets	441	415
Amortization of leasehold improvements	2	—
Change in operating lease liability	(442)	(404)
Change in fair value of warrant liability	66	—
Changes in operating assets and liabilities:		
Financed insurance premium	(3,105)	(4,435)
Prepaid expenses	359	(1,654)
Accounts payable	(4,927)	8,821
Accrued expenses and other current liabilities	(1,635)	(3,346)
Other liabilities	464	—
Net cash used in operating activities	(78,093)	(90,728)
INVESTING ACTIVITIES:		
Purchase of available-for-sale securities	(64,218)	(121,589)
Proceeds from sale of available-for-sale securities	—	5,538
Proceeds from maturities of available-for-sale securities	77,388	128,484
Net cash provided by investing activities	13,170	12,433
FINANCING ACTIVITIES:		
Proceeds from June Offering issuance of shares and prefunded warrants	27,811	—
Proceeds from February Offering, net of cash issuance costs of $169	—	74,421
Proceeds from financed insurance premium	3,105	4,434
Repayments of short-term borrowings	(3,273)	(4,718)
Exercise of stock options for common stock under Equity Incentive Plan	49	511
Exercise of Warrants	—	69
Net cash provided by financing activities	27,692	74,717
NET INCREASE (DECREASE) IN CASH AND CASH EQUIVALENTS	(37,231)	(3,578)
Cash and cash equivalents at beginning of period	53,888	57,466
Cash and cash equivalents at end of period	$ 16,657	$ 53,888
SUPPLEMENTAL DISCLOSURE OF CASH FLOW INFORMATION:		
Initial measurement of warrant liability	$ 21,835	$ —
Conversion of warrant liability to equity for warrant exercises	$ 1,417	$ —
Reclassification of prefunded warrant liability to equity	$ 6,827	$ —
Unrealized gain (loss) on marketable securities	$ 158	$ 5

The Notes to Financial Statements are an integral part of these statements.

NOTES TO AUDITED FINANCIAL STATEMENTS

1. ORGANIZATION AND SUMMARY OF SIGNIFICANT ACCOUNTING POLICIES

Operations and Business

Applied Therapeutics, Inc. (the "Company") is a clinical-stage biopharmaceutical company developing a pipeline of novel product candidates against validated molecular targets in indications of high unmet medical need. In particular, the Company is currently targeting treatments for CNS rare diseases and diabetic complications. The Company was incorporated in Delaware on January 20, 2016 and is headquartered in New York, New York.

On January 28, 2020, the Company completed its secondary public offering (the "Secondary Public Offering"), pursuant to which it issued and sold 2,741,489 shares of common stock at a public offering price of $45.50 per share, with an additional 411,223 shares sold pursuant to the underwriters' full exercise of their option to purchase additional shares. The aggregate net proceeds received by the Company from the offering, after deducting underwriting discounts and commissions and offering costs, were $134.1 million.

On June 4, 2020, the Company filed a shelf registration statement on Form S-3 (the "Shelf Registration Statement") under which the Company may, from time to time, sell securities in one or more offerings having an aggregate offering price of up to $300.0 million. The Shelf Registration Statement was declared effective as of June 15, 2020. As of the filing date of this Annual Report, the Company has sold 3,450,000 shares of common stock under the Shelf Registration.

On June 12, 2020, the Company entered into an equity distribution agreement (the "Goldman Equity Distribution Agreement") with Goldman Sachs & Co. LLC ("Goldman"), as a sales agent to sell shares of the Company's common stock, from time to time, having an aggregate offering price of up to $100 million. Goldman may act as an agent on the Company's behalf or purchase shares of the Company's common stock as a principal. As of December 31, 2021, the Company had not sold any shares of common stock pursuant to the Goldman Equity Distribution Agreement. This agreement has since been terminated as of January 24, 2022.

On February 17, 2021, the Company completed an underwritten public offering (the "February Offering") of 3,450,000 shares of common stock, including the exercise in full of the underwriters' option to purchase 450,000 additional shares of common stock, which option closed on February 19, 2021. The shares were offered at a price to the public of $23.00 per share, resulting in aggregate net proceeds of approximately $74.4 million, after deducting underwriting discounts and commissions and offering expenses.

On January 26, 2022, the Company entered into an equity distribution agreement (the "Cowen Equity Distribution Agreement) with Cowen and Company, LLC ("Cowen"), as a sales agent, to sell shares of the Company's common stock, from time to time, having an aggregate offering price of up to $100.0 million. Pursuant to the Cowen Equity Distribution Agreement shares of our common stock may be offered and sold through the sales agent in sales deemed "at-the-market" offerings under the Securities Act of 1933, as amended, or the Securities Act. Under the Cowen Equity Distribution Agreement, the sales agent will be entitled to compensation of up to 3% of the gross offering proceeds of all shares of our common stock sold through it pursuant to the Cowen Equity Distribution Agreement. In connection with the sale of shares of our common stock on our behalf, the sales agent may be deemed to be "underwriters" within the meaning of the Securities Act, and the compensation paid to the sales agent may be deemed to be underwriting commissions or discounts. As of December 31, 2022, the Company has not sold any shares of common stock pursuant to the Cowen Equity Distribution Agreement.

On June 27, 2022, the Company completed an underwritten public offering (the "June Offering") of 20,000,000 shares of common stock, par value $0.0001 per share, 10,000,000 pre-funded warrants to purchase shares of common stock (the "Pre-Funded Warrants"), and accompanying warrants to purchase up to 30,000,000 shares of common stock (the "Common Warrants"). The shares and accompanying Common Warrants were offered at a price to the public of $1.00 per share and warrant, and the Pre-Funded Warrants and accompanying Common Warrants were offered at a price to the public of $0.9999, resulting in aggregate net proceeds of approximately $27.8 million, after deducting

underwriting discounts and commissions and offering expenses. The Pre-Funded Warrants and the Common Warrants are immediately exercisable and will expire five years from the date of issuance. Holders may not exercise any Pre-Funded Warrants or Common Warrants that would cause the aggregate number of shares of common stock beneficially owned by the holder to exceed 9.99% of the Company's outstanding common stock immediately after exercise. Holders of the Pre-Funded Warrants and/or Common Warrants (together with affiliates) who immediately prior to June 27, 2022 beneficially owned more than 9.99% of the Company's outstanding common stock may not exercise any portion of their Pre-Funded Warrants or Common Warrants if the holder (together with affiliates) would beneficially own more than 19.99% of the Company's outstanding common stock after exercise. The Pre-Funded Warrants and Common Warrants are subject to adjustment in the event of certain stock dividends and distributions, stock splits, stock combinations, reclassifications or similar events affecting the common stock and also upon any distributions for no consideration of assets to the Company's stockholders. In the event of certain corporate transactions, the holders of the Pre-Funded Warrants and/or Common Warrants will be entitled to receive, upon exercise, the kind and amount of securities, cash or other property that the holders would have received had they exercised the Pre-Funded Warrants and/or Common Warrants immediately prior to such transaction. The Pre-Funded Warrants and Common Warrants do not entitle the holders thereof to any voting rights or any of the other rights or privileges to which the Company's stockholders are entitled. The Company intends to use the net proceeds from the June Offering for general corporate purposes, which may include research and development costs, including the conduct of clinical trials and process development and manufacturing of the Company's product candidates, expansion of the Company's research and development capabilities, working capital and capital expenditures.

Liquidity and Going Concern

The Company has incurred, and expects to continue to incur, significant operating losses for the foreseeable future as it continues to develop its drug candidates. To date, the Company has not generated any revenue, and it does not expect to generate revenue unless and until it successfully completes development and obtains regulatory approval for one of its product candidates.

Under ASC Topic 205-40, Presentation of Financial Statements - Going Concern, management is required at each reporting period to evaluate whether there are conditions and events, considered in the aggregate, that raise substantial doubt about an entity's ability to continue as a going concern within one year after the date that the financial statements are issued. We are actively pursuing several potential financing options. While we continue to explore opportunities to raise additional equity capital in the public markets, this has proven to be challenging in the biotech sector recently. Other options for structured finance which we continue to explore include a PIPE (private investment in public equity), debt, convertible debt, and synthetic royalty financing. Synthetic royalty financing, in particular, has become a favorable option for many companies for funding ongoing clinical development in late-stage and pre-approval programs. We have engaged an investment bank and we are specifically exploring this option in the near term. Additionally, we are in active dialogue with several potential partners regarding business development opportunities related to one or more of our programs. There can be no assurances that our discussions with any of the current counterparties will be successful, and the Company expects to continue to pursue additional opportunities.

As reflected in the accompanying financial statements, the Company incurred a net loss of $82.5 million for the year ended December 31, 2022 and has an accumulated deficit of $348.8 million as of December 31, 2022. The exclusive licensing agreement with Advanz Pharma for commercialization rights to AT-007 in Europe provides a source of capital to the Company based on clinical and regulatory milestones. We received a $10.7 million upfront payment from Advanz Pharma in January 2023 in conjunction with signing the agreement. If actualization of these milestones aligns with the projected timelines, and product approvals are received in the timeframes expected, this source of capital may be sufficient to cover operating expenses through expected product approvals and potential revenues. However, there are no guarantees that this will materialize timely or at all, and delays or unexpected data could disrupt this potential liquidity. Broadly, the Company has not yet established an ongoing source of revenues sufficient to cover its operating costs and is dependent on debt and equity financing to fund its operations. As of December 31, 2022, our cash, cash equivalents and marketable securities totaled $30.6 million. Given our planned expenditures for the next twelve months, we have concluded there is substantial doubt regarding our ability to continue as a going concern for a year beyond the date of these financial statements. The accompanying financial statements have been prepared assuming the continuation of the Company as a going concern.

Risks and Uncertainties

The Company is subject to risks common to companies in the biotechnology industry, including but not limited to, risks of failure of preclinical studies and clinical trials, the need to obtain marketing approval for any product candidate that it may identify and develop, the need to successfully commercialize and gain market acceptance of its product candidates, dependence on key personnel, protection of proprietary technology, compliance with government regulations, development by competitors of technological innovations and reliance on third party manufacturers.

Use of Estimates

The preparation of financial statements in conformity with U.S. GAAP requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities, disclosure of contingent assets and liabilities and the Company's ability to continue as a going concern as of the date of the financial statements and the reported amounts of expenses during the reporting period. In preparing the financial statements, management used estimates in the following areas, among others: prepaid and accrued expenses; warrant liability valuation; stock-based compensation expense; and the evaluation of the existence of conditions and events that raise substantial doubt regarding the Company’s ability to continue as a going concern. Actual results could differ from those estimates.

Significant Accounting Policies

Fair Value Measurements

Certain assets and liabilities are reported on a recurring basis at fair value. Fair value is defined as the exchange price that would be received for an asset or paid to transfer a liability (an exit price) 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. Financial assets and liabilities carried at fair value are to be classified and disclosed in one of the following three levels of the fair value hierarchy, of which the first two are considered observable and the last is considered unobservable:

Level 1—Quoted prices in active markets for identical assets or liabilities.

Level 2—Observable inputs (other than Level 1 quoted prices), such as quoted prices in active markets for similar assets or liabilities, quoted prices in markets that are not active for identical or similar assets or liabilities, or other inputs that are observable or can be corroborated by observable market data.

Level 3—Unobservable inputs that are supported by little or no market activity and that are significant to determining the fair value of the assets or liabilities, including pricing models, discounted cash flow methodologies and similar techniques.

Cash and Cash Equivalents

The Company considers all short-term, highly liquid investments, with an original maturity of three months or less, to be cash equivalents. The Company maintains its cash in bank deposit accounts which, at times, may exceed federally insured limits. The Company has not experienced any losses in these accounts and does not believe it is exposed to any significant credit risk on cash and cash equivalents.

Investments

The Company has investments in marketable debt securities. The Company determines the appropriate classification of its investments at the date of purchase and reevaluates the classifications at the balance sheet date. Marketable debt securities with maturities of 12 months or less are classified as short-term. Marketable debt securities with maturities greater than 12 months are classified as long-term. The Company’s marketable securities are accounted for as available for sale (“AFS”). AFS securities are reported at fair value. Unrealized gains and losses, after applicable

income taxes, are reported in accumulated other comprehensive income/(loss). Realized gains or losses on the sale of marketable securities are determined using the specific identification method and are recorded as a component of other income (expense), net.

The Company conducts an other-than-temporary impairment ("OTTI") analysis on a quarterly basis or more often if a potential loss-triggering event occurs. The Company considers factors such as the duration, severity and the reason for the decline in value, the potential recovery period and whether the Company intends to sell. For AFS securities, the Company also considers whether (i) it is more likely than not that the Company will be required to sell the debt securities before recovery of their amortized cost basis and (ii) the amortized cost basis cannot be recovered as a result of credit losses.

Leases

At the inception of an arrangement, the Company determines if an arrangement is, or contains, a lease based on the unique facts and circumstances present in that arrangement. Lease classification, recognition, and measurement are then determined at the lease commencement date. For arrangements that contain a lease the Company (i) identifies lease and non-lease components, (ii) determines the consideration in the contract, (iii) determines whether the lease is an operating or financing lease; and (iv) recognizes lease right-of-use ("ROU") assets and liabilities. Lease liabilities and their corresponding ROU assets are recorded based on the present value of lease payments over the expected lease term. The interest rate implicit in lease contracts is typically not readily determinable and as such, the Company uses its incremental borrowing rate based on the information available at the lease commencement date, which represents an internally developed rate that would be incurred to borrow, on a collateralized basis, over a similar term, an amount equal to the lease payments in a similar economic environment.

Most leases include options to renew and, or, terminate the lease, which can impact the lease term. The exercise of these options is at the Company's discretion and the Company does not include any of these options within the expected lease term as the Company is not reasonably certain it will exercise these options. The Company has elected to combine lease components (for example fixed payments including rent) with non-lease components (for example, non-dedicated parking and common-area maintenance costs) on our real estate asset classes.

Fixed, or in substance fixed, lease payments on operating leases are recognized over the expected term of the lease on a straight-line basis. Fixed lease expense on operating leases is recognized within operating expenses within the statements of operations. The Company has operating leases for our corporate offices. The Company has elected the short-term lease exemption and, therefore, do not recognize a ROU asset or corresponding liability for lease arrangements with an original term of 12 months or less. Leasehold improvements and assets under financing lease arrangements are amortized over the lesser of the asset's estimated useful life or the term of the respective lease. Maintenance costs are expensed as incurred.

Operating leases are included in operating lease right-of-use asset, current portion of operating lease liabilities, and noncurrent portion of operating lease liabilities in the balance sheet as of December 31, 2022 and 2021.

Clinical hold-back, long-term

As part of the regulatory approval process for taking its products to market, the Company enters into certain Clinical Trial Agreements (CTAs) which include, among other things, the compensation and payment schedule the participating medical institutions and physicians will receive for all costs in connection with the clinical trial (or study) under the terms of the CTA. As individual patients are enrolled in the study by the participating medical institution or physician, the Company pays certain per study fees according to the CTA for the duration of the trial. As invoices are received by the Company from the medical institution or physician, the Company retains an agreed upon percentage of total invoiced costs, generally ranging between 5% - 10%, that is withheld from payment until the end of the study.

These retained amounts are recorded as clinical holdback, a liability, on the accompanying balance sheets, and all expenses incurred in connection with these CTA activities are expensed as services are provided, which are included as research and development expenses on the accompanying statements of operations.

The following table shows the activity within the clinical holdback liability accounts for the year ended December 31, 2022:

(in thousands)		
Balance as of December 31,2021	$	—
Clinical holdback retained		464
Clinical holdback paid		—
Balance as of December 31,2022	$	464
Less: clinical holdback current portion		—
Clinical holdback - long-term portion	$	464

There was no clinical holdback during the year ended December 31, 2021.

Deferred Offering Costs

The Company capitalizes certain legal, professional accounting and other third party fees that are directly associated with in-process equity financings as deferred offering costs until such financings are consummated. After consummation of the equity financing, these costs are recorded in the statement of stockholders' (deficit) equity as a reduction of proceeds generated as a result of the offering. Should a planned equity financing be abandoned, the deferred offering costs would be expensed immediately as a charge to operating expenses in the statement of operations.

As of December 31, 2022 and 2021, the Company did not have any deferred offering costs recorded in prepaid and other current assets.

Research and Development

The Company expenses all costs incurred in performing research and development activities. Research and development expenses include salaries and other related costs, materials and supplies, preclinical expenses, manufacturing expenses, contract services and other outside expenses. As part of the process of preparing the financial statements, the Company is required to estimate their accrued research and development expenses. The Company makes estimates of the accrued expenses as of each balance sheet date in the financial statements based on facts and circumstances known at that time. In addition, there may be instances in which payments made to the Company's vendors will exceed the level of services provided and result in a prepayment of the expense in which case such amounts are reflected as prepaid expenses and other current assets. In accruing service fees, the Company estimates the time period over which services will be performed and the level of effort to be expended in each period. If the actual timing of the performance of services or the level of effort varies from the estimate, the Company adjusts the accrual or the amount of prepaid expenses accordingly. Nonrefundable advance payments for goods or services to be received in the future for use in research and development activities are deferred and capitalized in prepaid expenses and other current assets. The capitalized amounts are expensed as the related goods are delivered or the services are performed.

Research and development costs also include costs incurred in connection with certain licensing arrangements. Before a compound receives regulatory approval, the Company records upfront and milestone payments made to third parties under licensing arrangements as expense. Upfront payments are recorded when incurred, and milestone payments are recorded when the specific milestone has been achieved. Once a compound receives regulatory approval, the Company will record any milestone payments in identifiable intangible assets, less accumulated amortization and, unless the asset is determined to have an indefinite life, the Company will amortize the payments on a straight-line basis over the remaining agreement term or the expected product life cycle, whichever is shorter.

General and Administrative

General and administrative expenses consist primarily of salaries and other related costs, including stock-based compensation, for personnel in the Company's executive and finance functions. General and administrative expenses also include professional fees for legal, accounting, auditing, tax and consulting services; travel expenses; and facility-related expenses, which include allocated expenses for rent and maintenance of facilities and other operating costs.

Commercial expenses consist of payroll expense for commercial personnel, as well as marketing, market research, market access, and other focused investments to support launch of drug candidates, generate evidence of commercial potential and value proposition, and maximize potential business development deal leverage. Commercial expenses are included in general and administrative expenses.

Stock-Based Compensation

The Company accounts for its stock-based compensation as expense in the statements of operations based on the awards' grant date fair values. The Company accounts for forfeitures as they occur by reversing any expense recognized for unvested awards.

The Company estimates the fair value of options granted using the Black-Scholes option pricing model. The Black-Scholes option pricing model requires inputs based on certain subjective assumptions, including (a) the expected stock price volatility, (b) the calculation of expected term of the award, (c) the risk-free interest rate and (d) expected dividends. Due to the lack of a public market for the Company's common stock and a lack of company-specific historical and implied volatility data, the Company has based its estimate of expected volatility on the historical volatility of a group of similar companies that are publicly traded. The historical volatility is calculated based on a period of time commensurate with the expected term assumption. The computation of expected volatility is based on the historical volatility of a representative group of companies with similar characteristics to the Company, including stage of product development and life science industry focus. The Company uses the simplified method as allowed by the Securities and Exchange Commission ("SEC") Staff Accounting Bulletin ("SAB") No. 107, Share-Based Payment, to calculate the expected term for options granted to employees as it does not have sufficient historical exercise data to provide a reasonable basis upon which to estimate the expected term. The risk-free interest rate is based on a treasury instrument whose term is consistent with the expected term of the stock options. The expected dividend yield is assumed to be zero as the Company has never paid dividends and has no current plans to pay any dividends on its common stock.

The fair value of stock-based payments is recognized as expense over the requisite service period which is generally the vesting period.

Stock-Based Compensation–Restricted Stock Units

The Company accounts for restricted stock units in accordance with the authoritative guidance for stock-based compensation. The fair value of restricted stock units is measured at the grant date based on the closing market price of the Company's common stock on the date of grant, and is recognized as expense on a straight-line basis over the period of vesting. Forfeitures are recognized as a reduction of stock-based compensation expense as they occur.

Income Taxes

The Company uses the asset and liability method of accounting for deferred income taxes. Under this method, deferred tax assets and liabilities are recognized for the expected future tax consequences of temporary differences between the carrying amounts and the tax basis of assets and liabilities at currently enacted tax rates. These temporary differences primarily relate to net operating loss carryforwards available to offset future taxable income. Valuation allowances are established, if necessary, to reduce a deferred tax asset to the amount that will more likely than not be realized.

The Company recognizes tax liabilities from an uncertain tax position only if it is more likely than not that the tax position will not be sustained upon examination by the taxing authorities, based on the technical merits of the tax position. There are no uncertain tax positions that have been recognized in the accompanying financial statements. The Company is required to file tax returns in the U.S. federal jurisdiction and in the states of New York, California, Massachusetts, New Jersey, and New York City. The Company's policy is to recognize interest and penalties related to uncertain tax benefits, if any, as part of income tax expense. No such interest and penalties have been accrued as of December 31, 2022 and 2021.

In December 2019, the FASB issued ASU 2019-12, *Income Taxes: Simplifying the Accounting for Income Taxes.* The new standard intended to simplify the accounting for income taxes by eliminating certain exceptions related to the approach for intraperiod tax allocation, the methodology for calculating income taxes in an interim period and the recognition of deferred tax liabilities for outside basis differences. The new guidance also simplifies aspects of the accounting for franchise taxes and enacted changes in tax laws or rates and clarifies the accounting for transactions that result in a step-up in the tax basis of goodwill. The standard is effective for annual periods beginning after December 15, 2020 and interim periods within, with early adoption permitted. Adoption of the standard requires certain changes to primarily be made prospectively, with some changes to be made retrospectively. The Company adopted the amendment on January 1, 2021, with no impact to the financial statements.

Net Loss per Share

Basic net loss per share is calculated by dividing net loss available to common stockholders by the weighted-average common stock outstanding. Diluted net loss per share is calculated similarly, except that it includes the dilutive effect of the assumed exercise of securities, including outstanding warrants and the effect of shares issuable under the Company's stock-based compensation plan, if such effect is dilutive.

Segment Information

Operating segments are defined as components of an enterprise for which separate discrete information is available for evaluation by the chief operating decision-maker in deciding how to allocate resources and assess performance. The Company and the Company's chief operating decision-maker, the Company's chief executive officer, views the Company's operations and manages its business as a single operating segment, which is the business of discovering and developing its product candidates.

Recent Accounting Pronouncements

Any recent pronouncements issued by the FASB or other authoritative standards groups with future effective dates are either not applicable or are not expected to be significant to the financial statements of the Company.

2. LICENSE AGREEMENT

Columbia University

In October 2016, the Company entered into a license agreement (the "2016 Columbia Agreement") with the Trustees of Columbia University ("Columbia University") to obtain an exclusive royalty-bearing sublicensable license in respect to certain patents. As part of the consideration for entering into the 2016 Columbia Agreement, the Company issued to Columbia University shares equal to 5% of its outstanding common stock on a fully diluted basis at the time of issue. The common stock had a fair value of $0.5 million at the time of issuance. The Company will be required to make further payments to Columbia University of up to an aggregate of $1.3 million for the achievement of specified development and regulatory milestones, and up to an aggregate of $1.0 million for the achievement of a specified level of aggregate annual net sales, in each case in connection with products covered by the 2016 Columbia Agreement. The Company will also be required to pay tiered royalties to Columbia University in the low- to mid-single digit percentages on the Company's, its affiliates' and its sublicensees' net sales of licensed products, subject to specified offsets and reductions. In addition, the Company is required to make specified annual minimum royalty payments to Columbia

University, which is contingent upon the approval of the licensed products, in the mid-six figures beginning on the 10th anniversary of the effective date of the 2016 Columbia Agreement. When we grant sublicenses under the 2016 Columbia Agreement we are required to pay Columbia University a portion of the net sublicensing revenue received from such third parties, at percentages between 10% and 20%, depending on the stage of development at the time such revenue is received from such third parties. The Advanz Agreement includes a sublicense under the 2016 Columbia Agreement.

The 2016 Columbia Agreement will terminate upon the expiration of all the Company's royalty payment obligations in all countries. The Company may terminate the 2016 Columbia Agreement for convenience upon 90 days' written notice to Columbia University. At its election, Columbia University may terminate the 2016 Columbia Agreement, or convert the licenses granted to the Company into non-exclusive, non-sublicensable licenses, in the case of (a) the Company's uncured material breach upon 30 days' written notice (which shall be extended to 90 days if the Company is diligently attempting to cure such material breach), (b) the Company's failure to achieve the specified development and funding milestone events, or (c) the Company's insolvency.

In January 2019, the Company entered into a second license agreement with Columbia University (the "2019 Columbia Agreement"). Pursuant to the 2019 Columbia Agreement, Columbia University granted the Company a royalty-bearing, sublicensable license that is exclusive with respect to certain patents, and non-exclusive with respect to certain know-how, in each case to develop, manufacture and commercialize PI3k inhibitor products. The license grant is worldwide. Under the 2019 Columbia Agreement, the Company is obligated to use commercially reasonable efforts to research, discover, develop and market licensed products for commercial sale in the licensed territory, and to comply with certain obligations to meet specified development and funding milestones within defined time periods. Columbia University retains the right to conduct, and grant third parties the right to conduct, non-clinical academic research using the licensed technology; provided that such research is not funded by a commercial entity or for-profit entity or results in rights granted to a commercial or for-profit entity. As consideration for entering into the 2019 Columbia Agreement, the Company made a nominal upfront payment to Columbia University. The Company will be required to make further payments to Columbia University of up to an aggregate of $1.3 million for the achievement of specified development and regulatory milestones, and up to an aggregate of $1.0 million for the achievement of a specified level of aggregate annual net sales, in each case in connection with products covered by the 2019 Columbia Agreement. The Company will also be required to pay tiered royalties to Columbia University in the low- to mid-single digit percentages on the Company's, its affiliates' and its sublicensees' net sales of licensed products, subject to specified offsets and reductions. In addition, the Company is required to make specified annual minimum royalty payments to Columbia University, which is contingent upon the approval of the licensed products, in the mid-six figures beginning on the tenth anniversary of the effective date of the 2019 Columbia Agreement.

In July 2022, following regulatory changes impacting development of the class of PI3k inhibitors and the Company's decision to discontinue its early stage preclinical PI3k program, the Company and Columbia entered into an agreement terminating the 2019 Columbia Agreement (the "2022 Columbia Termination Agreement") as of July 25, 2022. Under the terms of the 2022 Columbia Termination Agreement, the Company assigned certain regulatory documents regarding the preclinical PI3k inhibitor AT-104 to Columbia and granted Columbia a non-exclusive royalty free license (with rights to sublicense any future Columbia licensee) under certain know-how, technical information and data relating to AT-104 that was developed by the Company during the term of the 2019 Columbia Agreement.

In March 2019, and in connection with the 2016 Columbia Agreement, the Company entered into a research services agreement (the "2019 Columbia Research Agreement") with Columbia University with the purpose of analyzing structural and functional changes in brain tissue in an animal model of Galactosemia, and the effects of certain compounds whose intellectual property rights were licensed to the Company as part of the 2016 Columbia Agreement on any such structural and functional changes. The 2019 Columbia Research Agreement had a term of 12 months from its effective date and expired in accordance with its terms.

On October 3, 2019, and in connection with the 2019 Columbia Agreement, the Company entered into a research services agreement (the "PI3k Columbia Research Agreement" and collectively with the 2016 Columbia Agreement, 2019 Columbia Agreement and 2019 Columbia Research Agreement, the "Columbia Agreements") with Columbia

University with the purpose of analyzing PI3k inhibitors for the treatment of lymphoid malignancies. The PI3k Columbia Research Agreement had a term of 18 months from its effective date and expired in accordance with its terms.

During the years ended December 31, 2022 and 2021, the Company recorded $0 and $0 in research and development expense, respectively, and $0.2 million and $0.2 million, respectively, in general and administrative expense related to the Columbia Agreements. In aggregate, the Company has incurred $2.7 million in expense from the execution of the Columbia Agreements through December 31, 2022.

As of December 31, 2022, the Company had $0.1 million due to Columbia University included in accrued expenses and $0 included in accounts payable. As of December 31, 2021, the Company had $12,000 due to Columbia University included in accrued expenses and $0.1 million included in accounts payable.

University of Miami

2020 Miami License Agreement

On October 28, 2020, the Company entered into a license agreement with the University of Miami (the "2020 Miami License Agreement") relating to certain technology that is co-owned by the University of Miami (UM), the University of Rochester (UR) and University College London (UCL). UM was granted an exclusive agency from UR and UCL to license each of their rights in the technology. Pursuant to the 2020 Miami License Agreement, UM, on behalf of itself and UR and UCL, granted the Company a royalty-bearing, sublicensable license that is exclusive with respect to certain patent applications and patents that may grant from the applications, and non-exclusive with respect to certain know-how, in each case to research, develop, make, have made, use, sell and import products for use in treating and/or detecting certain inherited neuropathies, in particular those caused by mutation in the sorbitol dehydrogenase (SORD) gene. The license grant is worldwide. Under the 2020 Miami License Agreement, the Company is obligated to use commercially reasonable efforts to develop, manufacture, market and sell licensed products in the licensed territory, and to comply with certain obligations to meet specified development milestones within defined time periods. UM retains for itself, UR, and UCL the right to use the licensed patent rights and licensed technology for their internal non-commercial educational, research and clinical patient care purposes, including in sponsored research and collaboration with commercial entities.

Under the terms of the 2020 Miami License Agreement, the Company was obligated to pay UM an up-front non-refundable license fee of $1.1 million, and a second non-refundable license fee of $0.5 million due on the first anniversary of the date of the license. The Company will be required to make further payments to UM of up to an aggregate $2.2 million for the achievement of specified patenting and development milestones, and up to an aggregate of $4.1 million for achievement of late stage regulatory milestones. The Company will also be required to pay royalties ranging from 0.88% - 5% on the Company's, the Company's affiliates' and the Company's sublicensees' net sales of licensed products. When the Company sublicenses the rights granted under the 2020 Miami License Agreement to one or more third parties, the Company will be required to pay to UM a portion of the non-royalty sublicensing revenue received from such third parties ranging from 15% – 25%. The Advanz Agreement includes a sublicense under the 2020 Miami License Agreement.

The 2020 Miami License Agreement terminates upon the expiration of all issued patents and filed patent applications or 10 years after the first commercial sale of the last product or process for which a royalty is due, unless earlier terminated. In addition, the 2020 Miami License Agreement may be terminated by the Company at any time upon 60 days prior written notice to UM, and may be terminated by either the Company or UM upon material breach of an obligation if action to cure the breach is not initiated within 60 days of receipt of written notice.

The Company recorded $0.1 million and $0 in research and development expense and general and administrative expense, respectively, during the year-ended December 31, 2022. As of December 31, 2022, the Company had $0.3 million in accrued expenses.

The Company recorded $0.03 million and $0 in research and development expense and general and administrative expense, respectively, during the year-ended December 31, 2021. As of December 31, 2021, the Company had $0.3 million in accrued expenses.

2020 Miami Option Agreement

On October 28, 2020, the Company entered into an option agreement with the University of Miami (the "2020 Miami Option Agreement") concerning certain research activities and technology relating to SORD neuropathy that may be pursued and developed by UM. Under the 2020 Miami Option Agreement, if UM conducts such research activities, then UM is obligated to grant us certain option rights to access and use the research results and to obtain licenses to any associated patent rights upon us making specified payments to UM within specified time limits. If the Company elects to obtain option rights the Company will be required to make payments to UM in the low-six figures to the low-seven figures, depending upon the rights the Company elects to obtain, and the Company will be obligated to make certain milestone payments in the high-six figures to mid-seven figures if UM conducts and completes certain research activities within specified time periods and the Company elects to receive rights to use the results of that research.

2020 Miami Sponsored Research Agreement

On December 14, 2020, the Company entered into a research agreement with the University of Miami (the "2020 Miami Research Agreement"), under which the University of Miami will conduct a research study relating to SORD neuropathy and deliver a final report on the study to the Company. The term of the research agreement was from December 14, 2020 through December 30, 2021, and was extended through August 31, 2022. The total consideration for the 2020 Miami Research Agreement was $0.3 million.

During the years ended December 31, 2022 and 2021, the Company recorded $48,000 and $0.2 million in research and development expenses, respectively, in relation to the 2020 Miami Research Agreement. As of December 31, 2022 and 2021, the Company had $1.0 million and $0.2 million, respectively, in accrued expenses.

Bayh-Dole Act

Some of the intellectual property rights the Company has licensed, including certain rights licensed in the agreements described above, may have been generated through the use of U.S. government funding. As a result, the U.S. government may have certain rights to intellectual property embodied in the Company's current or future product candidates under the Bayh-Dole Act of 1980, or Bayh-Dole Act, including the grant to the government of a non-exclusive, worldwide, freedom to operate license under any patents, and the requirement, absent a waiver, to manufacture products substantially in the United States. To the extent any of the Company's current or future intellectual property is generated through the use of U.S. government funding, the provisions of the Bayh-Dole Act may similarly apply.

3. FAIR VALUE MEASUREMENTS

The following tables summarize, as of December 31, 2022 and 2021, the Company's financial assets and liabilities that are measured at fair value on a recurring basis, according to the fair value hierarchy described in the significant accounting policies section.

	As of December 31, 2022			
(in thousands)	Level 1	Level 2	Level 3	Total
Cash	$ 1,337	$ —	$ —	$ 1,337
Money market funds	15,320	—	—	15,320
Total cash and cash equivalents	$ 16,657	$ —	$ —	$ 16,657
U.S. government agency debt securities	—	13,923	—	13,923
Total marketable securities	$ —	$ 13,923	$ —	$ 13,923
Total financial assets measured at fair value on a recurring basis	$ 16,657	$ 13,923	$ —	$ 30,580
Warrant liabilities - Common Warrants	—	—	13,657	13,657
Total financial liabilities measured at fair value on a recurring basis	$ —	$ —	$ 13,657	$ 13,657

	As of December 31, 2021			
(in thousands)	Level 1	Level 2	Level 3	Total
Cash	$ 12,671	$ —	$ —	$ 12,671
Money market funds	41,217	—	—	41,217
Total cash and cash equivalents	$ 53,888	$ —	$ —	$ 53,888
U.S. government agency debt securities	—	26,935	—	26,935
Total marketable securities	$ —	$ 26,935	$ —	$ 26,935
Total financial assets measured at fair value on a recurring basis	$ 53,888	$ 26,935	$ —	$ 80,823

Investments in certificate of deposits, corporate bonds, and U.S. government agency debt securities have been classified as Level 2 as they are valued using quoted prices in less active markets or other directly or indirectly observable inputs. Fair values of corporate bonds and U.S. government agency debt securities were derived from a consensus or weighted average price based on input of market prices from multiple sources at each reporting period. With regard to commercial paper, all of the securities had high credit ratings and one year or less to maturity; therefore, fair value was derived from accretion of purchase price to face value over the term of maturity or quoted market prices for similar instruments if available. During the period ended December 31, 2022 and 2021, there were no transfers of financial assets between Level 1 and Level 2.

On June 27, 2022 the Company issued Common Warrants exercisable for 30,000,000 shares of common stock and Pre-Funded Warrants exercisable for 10,000,000 shares of common stock in connection with the June Offering (see note 1 and note 8 for more information on the June Offering). The Common Warrants were accounted for as liabilities under ASC 815-40, *Derivatives and Hedging, Contracts in Entity's Own Equity* ("ASC 815-40"), as these warrants provide for a settlement provision that does not meet the requirements of the indexation guidance under ASC 815-40. The Pre-Funded Warrants were initially recorded at fair value as a liability as the Company could be required to settle the Pre-Funded Warrants in cash under certain circumstances. In December 2022, the Company amended the Pre-Funded Warrants to remove the potential requirement that they could be settled in cash under certain circumstances. Upon the amendment to the Pre-Funded Warrants, the Pre-funded Warrants liability was reclassified to equity, using their fair value as of the amendment date.

These Common Warrant liabilities were measured at fair value at inception and are then subsequently measured on a recurring basis, with changes in fair value recognized in other income (expense) within the Company's statement of operations.

The Company uses a Black-Scholes option pricing model to estimate the fair value of the Common and Pre-Funded Warrants, which utilizes certain unobservable inputs and is therefore considered a Level 3 fair value measurement. Certain inputs used in this Black-Scholes pricing model may fluctuate in future periods based upon factors that are outside of the Company's control, including a potential change in control outside of the Company's control. A significant change in one or more of these inputs used in the calculation of the fair value may cause a significant change to the fair value of the Company's warrant liabilities, which could also result in material non-cash gains or losses being reported in the Company's consolidated statement of operations.

The Common and Pre-Funded Warrants were initially valued and remeasured using a Black-Scholes option pricing model with a range of assumptions as follows:

Expected term (in years)	3.7
Volatility	91.53 %
Risk-free interest rate	4.11 %
Dividend yield	0.00 %

The Company utilized a probability-weighted approach that considered the probability of a change in control at the Company in the Black-Scholes option pricing model, whereby a 10% probability of change in control was used for each of the five years in the term of the agreements.

The following table provides a roll forward of the aggregate fair values of the Company's warrant liability, for which fair value is determined using Level 3 inputs (in thousands):

	Warrant Liability	
	Common Warrant	Pre-Funded Warrant
Balance as of January 1, 2022	$ —	$ —
Initial fair value of Warrant Liability	13,734	8,101
Warrants exercised	—	(1,417)
Change in fair value	(77)	143
Reclassification of pre-funded warrant liability to equity		(6,827)
Balance as of December 31, 2022	$ 13,657	$ —

The inputs utilized by management to value the warrant liability for Common and Pre-Funded Warrants are highly subjective. The assumptions used in calculating the fair value of the warrant liability for Common and Pre-Funded Warrants represent the Company's best estimates, but these estimates involve inherent uncertainties and the application of management judgment. As a result, if factors change and the Company uses different assumptions, the fair value of the warrant liability for Common Warrants may be materially different in the future.

4. INVESTMENTS

Marketable Securities

Marketable securities, which the Company classifies as available-for-sale securities, primarily consist of high quality commercial paper, corporate bonds, and U.S. government debt obligations. Marketable securities with remaining effective maturities of twelve months or less from the balance sheet date are classified as short-term; otherwise, they are classified as long-term on the balance sheets.

The following tables provide the Company's marketable securities by security type (in thousands):

	As of December 31, 2022				As of December 31, 2021			
(in thousands)	Cost	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value	Cost	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value
US government agency debt security	$ 13,873	$ 50	$ —	$ 13,923	$ 27,042	$ 1	$ (108)	$ 26,935
Total	$ 13,873	$ 50	$ —	$ 13,923	$ 27,042	$ 1	$ (108)	$ 26,935

As of December 31, 2022, the Company's investment portfolio reported no unrealized loss. Based on its evaluations, the Company determined that a credit loss allowance is not required since the decline was not related to underlying credit issues of the counterparties. The counterparties to these investments have high credit quality with investment grade ratings of at least AA+ or above, along with a history of no defaults. No single investment in the portfolio had an individually material unrealized loss and in the aggregate. In addition, the Company does not intend to sell these investments and it is not more likely than not that the Company will be required to sell these investments before recovery of their amortized cost bases. Accordingly, based on the foregoing evaluation, the Company did not record any credit losses during the year ended December 31, 2022 and 2021. Unrealized gains are also reflected, net of tax, as other comprehensive income (loss) in the Statements of Comprehensive Loss.

Contractual maturities of the Company's marketable securities are summarized as follows (in thousands):

	As of December 31, 2022				As of December 31, 2021			
(in thousands)	Cost	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value	Cost	Gross Unrealized Gains	Gross Unrealized Losses	Estimated Fair Value
Due in one year or less	$ 13,873	$ 50	$ —	$ 13,923	$ 27,042	$ 1	$ (108)	$ 26,935
Due in one through two years	—	—	—	—	—	—	—	—
Total	$ 13,873	$ 50	$ —	$ 13,923	$ 27,042	$ 1	$ (108)	$ 26,935

At December 31, 2022, the Company had $50,000 of gross unrealized gains and $0 of gross unrealized losses primarily due to fluctuations in the fair value of certain U.S. government agency debt securities.

During the year ended December 31, 2022, the Company recorded gross realized losses of $0.2 million and gross realized gains of $16,000 from the redemption of marketable securities.

The unrealized losses and fair values of available-for-sale securities that have been in an unrealized loss position for a period of less than and greater than 12 months as of December 31, 2022 are as follows:

	As of December 31, 2022					
	Securities in an unrealized loss position less than 12 months		Securities in an unrealized loss position greater than 12 months		Total	
(in thousands)	Unrealized Losses	Estimated Fair Value	Unrealized Losses	Estimated Fair Value	Unrealized Losses	Estimated Fair Value
US government agency debt security	$ —	$ —	$ —	$ —	$ —	$ —
Total	$ —	$ —	$ —	$ —	$ —	$ —

The unrealized losses and fair values of available-for-sale securities that have been in an unrealized loss position for a period of less than and greater than 12 months as of December 31, 2021 are as follows:

	As of December 31, 2021					
	Securities in an unrealized loss position less than 12 months		Securities in an unrealized loss position greater than 12 months		Total	
(in thousands)	Unrealized Losses	Estimated Fair Value	Unrealized Losses	Estimated Fair Value	Unrealized Losses	Estimated Fair Value
US government agency debt security	$ (108)	$ 17,696	$ —	$ —	$ (108)	$ 17,696
Total	$ (108)	$ 17,696	$ —	$ —	$ (108)	$ 17,696

5. PREPAID EXPENSE AND OTHER CURRENT ASSETS

Prepaid expenses and other current assets consisted of the following (in thousands):

(in thousands)	December 31, 2022	December 31, 2021
Prepaid research and development expenses	$ 4,272	$ 4,483
Insurance premium asset	1,131	1,616
Prepaid rent expenses	99	117
Prepaid insurance expenses	71	105
Prepaid commercial and patient advocacy	206	254
Research and development tax credit receivable	252	502
Interest receivable	23	23
Other prepaid expenses and current assets	674	471
Total prepaid expenses & other current assets	$ 6,728	$ 7,571

6. ACCRUED EXPENSE AND OTHER CURRENT LIABILITIES

Accrued expenses and other current liabilities consisted of the following (in thousands):

(in thousands)	December 31, 2022	December 31, 2021
Accrued pre-clinical and clinical expenses	$ 8,877	$ 9,912
Short-term insurance financing note	622	789
Accrued professional fees	1,218	419
Accrued compensation and benefits	2,301	2,779
Accrued commercial expenses	896	1,394
Accrued patent expenses	361	279
Other	481	987
Total accrued expenses & other current liabilities	$ 14,756	$ 16,559

7. STOCK-BASED COMPENSATION

Equity Incentive Plans

In May 2019, the Company's board of directors (the "Board") adopted its 2019 Equity Incentive Plan ("2019 Plan"), which was subsequently approved by its stockholders and became effective on May 13, 2019. As a result, no additional awards under the Company's 2016 Equity Incentive Plan, as amended (the "2016 Plan") will be granted and all outstanding stock awards granted under the 2016 Plan that are repurchased, forfeited, expired or are cancelled will become available for grant under the 2019 Plan in accordance with its terms. The 2016 Plan will continue to govern outstanding equity awards granted thereunder.

The 2019 Plan provides for the issuance of incentive stock options ("ISOs") to employees, and for the grant of nonstatutory stock options, stock appreciation rights, restricted stock awards, restricted stock unit awards, performance stock awards, performance cash awards and other forms of stock awards to the Company's employees, officers and directors, as well as non- employees, consultants and affiliates to the Company. Under the terms of the 2019 Plan, stock options may not be granted at an exercise price less than fair market value of the Company's common stock on the date of the grant. The 2019 Plan is administered by the Compensation Committee of the Company's Board.

Initially, subject to adjustments as provided in the 2019 Plan, the maximum number of the Company's common stock that may be issued under the 2019 Plan is 4,530,000 shares, which is the sum of (i) 1,618,841 new shares, plus (ii) the number of shares (not to exceed 2,911,159 shares) that remained available for the issuance of awards under the 2016 Plan, at the time the 2019 Plan became effective, and (iii) any shares subject to outstanding stock options or other stock awards granted under the 2016 Plan that are forfeited, expired, or reacquired. The 2019 Plan provides that the number of shares reserved and available for issuance under the 2019 Plan will automatically increase each January 1, beginning on January 1, 2020, by 5% of the outstanding number of shares of common stock on the immediately preceding December 31 or such lesser number of shares as determined by the Board. Subject to certain changes in capitalization of the Company, the aggregate maximum number of shares of common stock that may be issued pursuant to the exercise of ISOs shall be equal to 13,000,000 shares of common stock. Stock options awarded under the 2019 Plan expire 10 years after grant and typically vest over four years.

On August 2, 2022, the Board took action in accordance with its authority under the terms of the 2019 Plan to reset the per-share exercise price of all stock options previously granted under the 2019 Plan to $1.05 per share (the "Options Repricing"), which is equal to the closing price of a share of the Company’s common stock on August 1, 2022. The Options Repricing was deemed to be a Type I modification event under ASC 718, *Compensation-Stock Compensation*. No other terms of the repriced stock options were modified, and the repriced stock options will continue to vest according to their original vesting schedules and will retain their original expiration dates. As a result of the

Options Repricing, 1,797,517 vested and 1,380,917 unvested stock options outstanding as of August 2, 2022, with original exercise prices ranging from $1.22 to $49.60, were repriced. The Options Repricing resulted in incremental stock-based compensation expense of $1.4 million, of which $0.9 million related to vested stock option awards and was expensed on the repricing date, and $0.5 million of which related to unvested stock option awards and is being amortized on a ratable basis over the remaining weighted-average vesting period of those awards being approximately 2.4 years.

As of December 31, 2022, there were 1,096,493 shares of common stock available for issuance under the 2019 Plan. On January 1, 2023, there were 2,403,167 shares that became issuable for future grants subject to the adjustments provided in the 2019 Plan.

Stock-Based Compensation Expense

Total stock-based compensation expense recorded for employees, directors and non-employees (in thousands):

	Year Ended December 31,	
(in thousands)	**2022**	**2021**
Research and development	$ 3,619	$ 2,759
General and administrative	5,543	8,418
Total stock-based compensation expense	$ 9,162	$ 11,177

Stock Option Activity

During the year ended December 31, 2022, and 2021 the Company granted options to purchase 767,913 and 406,752 shares of common stock, respectively. For the years ended December 31, 2022, and 2021, amortization of stock compensation of options amounted to $7.8 million and $9.3 million, respectively. As of December 31, 2022, the total unrecognized stock-based compensation balance for unvested options was $8.1 million, which is expected to be recognized over 2.2 years. The weighted-average fair value of options granted during the years ended December 31, 2022, and December 31, 2021, were $1.79 per share and $8.43 per share, respectively.

The following table summarizes the information about options outstanding at December 31, 2022:

(in thousands, except for share data)	**Options Outstanding**	**Weighted-Average Exercise Price**	**Weighted-Average Remaining Contractual Term (in years)**	**Aggregate Intrinsic Value**
Outstanding at December 31, 2021	4,704,888	$ 13.29	7.7	$ 10,305
Options granted	767,913	1.39		
Options exercised	(47,602)	1.04		21
Forfeited	(377,378)	19.90		
Expired	(173,774)	26.82		
Outstanding at December 31, 2022	4,874,047	$ 1.97	6.9	$ —
Exercisable at December 31, 2022	3,859,880	$ 2.21	6.6	$ —
Nonvested at December 31, 2022	1,014,167	$ 1.05	8.3	$ —

Valuation of Stock Options Granted to Employees that Contain Service Conditions Only

The fair value of each option award granted with service-based vesting is estimated on the date of the grant using the Black-Scholes option valuation model based on the weighted average assumptions noted in the table below for those options granted in the years ended December 31, 2022 and 2021.

	Year Ended December 31,	
	2022	2021
Expected term (in years)	5.7	5.8
Volatility	75.83 %	71.92 %
Risk-free interest rate	2.13 %	1.08 %
Dividend yield	— %	— %

Restricted Stock Unit Activity

During the year ended December 31, 2022, the Company granted 605,600 restricted stock units ("RSUs"). For the years ended December 31, 2022 and December 31, 20201 amortization of stock compensation of RSUs amounted to $1.3 million and $1.9 million, respectively. As of December 31, 2022, the unamortized compensation costs associated with non-vested restricted stock awards was $3.5 million with a weighted-average remaining amortization period of 3.2 years.

The following table summarizes the information about restricted stock units outstanding at December 31, 2022:

(in thousands, except for share data)	Shares	Weighted-Average Grant Date Fair Value	Aggregate Intrinsic Value
Outstanding at December 31, 2021	469,485	$ 18.05	$ 4,202
Awarded	605,600	2.33	
Released	(50,242)	24.57	
Forfeited	(209,334)	18.10	
Outstanding at December 31, 2022	815,509	$ 5.96	$ 620
Nonvested at December 31, 2022	815,509	$ 5.73	$ 582
Weighted Average Remaining Recognition Period (in years)	3.2		

2019 Employee Stock Purchase Plan

In May 2019, the Company's Board and its stockholders approved the 2019 Employee Stock Purchase Plan (the "ESPP"), which became effective as of May 13, 2019. The ESPP is intended to qualify as an "employee stock purchase plan" within the meaning of Section 423 of the U.S. Internal Revenue Code of 1986, as amended. The number of shares of common stock initially reserved for issuance under the ESPP was 180,000 shares. The ESPP provides for an annual increase on the first day of each year beginning in 2020 and ending in 2029, in each case subject to the approval of the Board, equal to the lesser of (i) 1% of the shares of common stock outstanding on the last day of the calendar month before the date of the automatic increase and (ii) 360,000 shares; provided that prior to the date of any such increase, the Board may determine that such increase will be less than the amount set forth in clauses (i) and (ii). As of December 31, 2022, no shares of common stock had been issued under the ESPP. The first offering period has not yet been decided by the Board.

8. STOCKHOLDERS' EQUITY

As of December 31, 2022, the authorized capital stock of the Company consists of 200,000,000 shares of common stock, par value $0.0001 per share and 10,000,000 shares of preferred stock, par value $0.0001 per share. As of

December 31, 2021, the authorized capital stock of the Company consists of 100,000,000 shares of common stock, par value $0.0001 per share and 10,000,000 shares of preferred stock, par value $0.0001 per share.

Common Stock

Voting

The holders of the common stock are entitled to one vote for each share of common stock held at all meetings of the stockholders. There is no cumulative voting.

Goldman Equity Distribution Agreement

In June 2020, the Company entered into the Goldman Equity Distribution Agreement to sell shares of the Company's common stock, from time to time, having an aggregate offering price of up to $100.0 million. The issuance and sale of shares of common stock by the Company pursuant to the Goldman Equity Distribution Agreement is deemed an "at-the-market" offering under the Securities Act of 1933, as amended, or the Securities Act. Goldman is entitled to compensation for its services equal to up to 3.0% of the gross offering proceeds of all shares of the Company's common stock sold through it as a sales agent pursuant to the Goldman Equity Distribution Agreement. The Goldman Equity Distribution Agreement was terminated as of January 24, 2022.

Cowen Equity Distribution Agreement

On January 26, 2022, the Company entered into the Cowen Equity Distribution Agreement to sell shares of the Company's common stock, from time to time, having an aggregate offering price of up to $100.0 million. Pursuant to the Cowen Equity Distribution Agreement shares of our common stock may be offered and sold through the sales agent in sales deemed "at-the-market" offerings under the Securities Act of 1933, as amended, or the Securities Act. Under the Cowen Equity Distribution Agreement, the sales agent will be entitled to compensation of up to 3% of the gross offering proceeds of all shares of our common stock sold through it pursuant to the Cowen Equity Distribution Agreement. In connection with the sale of shares of our common stock on our behalf, the sales agent may be deemed to be "underwriters" within the meaning of the Securities Act, and the compensation paid to the sales agent may be deemed to be underwriting commissions or discounts. As of December 31, 2022, the Company has not sold any shares of common stock pursuant to the Cowen Equity Distribution Agreement.

June 2022 Offering

On June 27, 2022, the Company completed the June Offering, an underwritten public offering of 20,000,000 shares of common stock, par value $0.0001 per share, 10,000,000 Pre-Funded Warrants, and accompanying Common Warrants to purchase up to 30,000,000 shares of common stock. The shares and accompanying Common Warrants were offered at a price to the public of $1.00 per share and warrant, and the Pre-Funded Warrants and accompanying Common Warrants were offered at a price to the public of $0.9999, resulting in aggregate net proceeds of approximately $27.8 million, after deducting underwriting discounts and commissions and offering expenses. The Pre-Funded Warrants and the Common Warrants are immediately exercisable and will expire five years from the date of issuance. Holders may not exercise any Pre-Funded Warrants or Common Warrants that would cause the aggregate number of shares of common stock beneficially owned by the holder to exceed 9.99% of the Company's outstanding common stock immediately after exercise. Holders of the Pre-Funded Warrants and/or Common Warrants (together with affiliates) who immediately prior to June 27, 2022 beneficially owned more than 9.99% of the Company's outstanding common stock may not exercise any portion of their Pre-Funded Warrants or Common Warrants if the holder (together with affiliates) would beneficially own more than 19.99% of the Company's outstanding common stock after exercise. The Pre-Funded Warrants and Common Warrants are subject to adjustment in the event of certain stock dividends and distributions, stock splits, stock combinations, reclassifications or similar events affecting the common stock and also upon any distributions for no consideration of assets to the Company's stockholders. In the event of certain corporate transactions, the holders of the Pre-Funded Warrants and/or Common Warrants will be entitled to receive, upon exercise, the kind and amount of securities, cash or other property that the holders would have received had they exercised the Pre-Funded Warrants and/or Common Warrants immediately prior to such transaction. The Pre-Funded Warrants and Common Warrants do

not entitle the holders thereof to any voting rights or any of the other rights or privileges to which the Company's stockholders are entitled. The Company intends to use the net proceeds from the June Offering for general corporate purposes, which may include research and development costs, including the conduct of clinical trials and process development and manufacturing of the Company's product candidates, expansion of the Company's research and development capabilities, working capital and capital expenditures.

9. WARRANTS

Warrants Issued with Series A Preferred Stock

On January 26, 2017, in connection with the sale and issuance of the Series A Preferred Stock, the Company issued equity-classified warrants to purchase 309,389 shares of common stock (the "2017 Warrants"), valued at $0.2 million, and included in the issuance costs of the Series A Preferred Stock. The warrants vested immediately and have an exercise price of $2.49 per share and expire on March 13, 2027.

The fair value of warrants issued is estimated using the Black-Scholes option pricing model with the following assumptions for the 2017 Warrants.

Contractual term (in years)	10.0
Volatility	74.48 %
Risk-free interest rate	3.20 %
Dividend yield	0.00 %

On December 5, 2019, an optionholder exercised 20,000 options in a cashless exercise at net, and the Company issued 17,026 shares of common stock.

On February 21, 2020, two warrantholders exercised 185,634 options in a cashless exercise at net, and the Company issued 176,092 shares of common stock. On February 24, 2020, a warrantholder exercised 72,818 options in a cashless exercise at net, and the Company issued 69,094 shares of common stock.

On February 5, 2021, a warrantholder exercised 27,855 warrants on a cash basis and received 27,855 shares of common stock. The Company received $69,000 in cash proceeds for the exercise of these warrants.

Warrants Issued with the 2018 Notes

On January 18, 2018, the Company entered into a placement agent agreement through which it became obligated to issue common stock warrants in connection with the issuance of the Company's convertible promissory notes issued on February 5, 2018 (the "2018 Notes"). The obligation to issue the 2018 Notes Warrants was recorded as a liability at its fair value (see Note 3), which was initially $0.1 million, and was included in the issuance costs of the 2018 Notes. On November 5, 2018, in connection with the extinguishment of the 2018 Notes into shares of Series B Preferred Stock, the Company issued the 2018 Notes Warrants, which were equity-classified warrants upon issuance, to purchase 76,847 shares of common stock, valued at $0.3 million. The 2018 Notes Warrants vested immediately upon issuance and have an exercise price of $6.59 per share and expire on November 4, 2028.

On February 24, 2020, a warrantholder exercised 386 options in a cashless exercise at net, and the Company issued 333 shares of common stock. On June 24, 2020, a warrantholder exercised 20,331 options in a cashless exercise at net, and the Company issued 17,369 shares of common stock.

Warrants Issued with Series B Preferred Stock

In November and December 2018, in connection with the sale and issuance of the Series B Preferred Stock, the Company was obligated to issue equity-classified warrants to purchase 72,261 shares of common stock (collectively the "2018 Warrants"), valued in the aggregate at $0.2 million, which was included in the issuance costs for the Series B

Preferred Stock. The warrants vest immediately upon issuance, have an exercise price of $8.24 per share and expire 10 years from the date of issuance.

The fair value of the 2018 Warrants is estimated using the Black-Scholes option pricing model with the following assumptions:

Contractual term (in years)	10.0
Volatility	73.22 %
Risk-free interest rate	2.70 %
Dividend yield	0.00 %

In February 2019, in connection with the sale and issuance of the Series B Preferred Stock, the Company was obligated to issue warrants to purchase 23,867 shares of common stock (collectively the "2019 Warrants"), valued in the aggregate at $0.1 million, which was included in the issuance costs for the Series B Preferred Stock. The warrants vest immediately upon issuance, have an exercise price of $8.24 per share and expire 10 years from the date of issuance.

The fair value of the 2019 Warrants was estimated using the Black-Scholes option pricing model with the following assumptions:

Contractual term (in years)	10.0
Volatility	73.22 %
Risk-free interest rate	2.70 %
Dividend yield	0.00 %

The inputs utilized by management to value the warrants are highly subjective. The assumptions used in calculating the fair value of the warrants represent the Company's best estimates, but these estimates involve inherent uncertainties and the application of management judgment. As a result, if factors change and the Company uses different assumptions, the fair value of the warrants may be materially different in the future.

Warrants Issued with June 2022 Offering

On June 27, 2022, in connection with the sale and issuance common stock as part of the June Offering, the Company issued 10,000,000 Pre-Funded Warrants at an exercise price of $0.0001 per share, and 30,000,000 accompanying Common Warrants at an exercise price of $1.00 per share. Each share of common stock and accompanying Common Warrant was sold at a public offering price of $1.00, less underwriting discounts and commissions, and each Pre-Funded Warrant and accompanying Common Warrant was sold at a public offering price of $0.9999, less underwriting discounts and commissions, as described in the prospectus supplement, dated June 22, 2022, filed with the Securities and Exchange Commission on June 24, 2022.

The Pre-Funded Warrants and the Common Warrants are immediately exercisable and will expire five years from the date of issuance. Holders may not exercise any Pre-Funded Warrants or Common Warrants that would cause the aggregate number of shares of common stock beneficially owned by the holder to exceed 9.99% of the Company's outstanding common stock immediately after exercise. Holders of the Pre-Funded Warrants and/or Common Warrants (together with affiliates) who immediately prior to June 27, 2022 beneficially owned more than 9.99% of the Company's outstanding common stock may not exercise any portion of their Pre-Funded Warrants or Common Warrants if the holder (together with affiliates) would beneficially own more than 19.99% of the Company's outstanding common stock after exercise. The Pre-Funded Warrants and Common Warrants are subject to adjustment in the event of certain stock dividends and distributions, stock splits, stock combinations, reclassifications or similar events affecting the common stock and also upon any distributions for no consideration of assets to the Company's stockholders. In the event of certain corporate transactions, the holders of the Pre-Funded Warrants and/or Common Warrants will be entitled to receive, upon exercise, the kind and amount of securities, cash or other property that the holders would have received had they exercised the Pre-Funded Warrants and/or Common Warrants immediately prior to such transaction. The Pre-

Funded Warrants and Common Warrants do not entitle the holders thereof to any voting rights or any of the other rights or privileges to which the Company's stockholders are entitled.

On June 28, 2022, a warrantholder exercised 1,750,000 Pre-Funded Warrants on a cash basis and received 1,750,000 shares of common stock. The Company received $175 in cash proceeds for the exercise of these Pre-Funded Warrants.

As of December 31, 2022, the Company had 8,250,000 Pre-Funded Warrants outstanding with a weighted average exercise price of $0.0001 per share and an average contractual life of 5 years. As of December 31, 2022, the Company had 30,000,000 Common Warrants outstanding with a weighted average exercise price of $1.00 per share and an average contractual life of 5 years.

The Common Warrants were accounted for as liabilities under ASC 815-40, as these warrants provide for a settlement provision that does not meet the requirements of the indexation guidance under ASC 815-40. These warrant liabilities are measured at fair value at inception and on a recurring basis, with changes in fair value presented within the statement of operations. The Pre-Funded Warrants were initially recorded at fair value as a liability as the Company could be required to settle the Pre-Funded Warrants in cash in the event of an acquisition of the Company under certain circumstances. In December 2022, the Company amended the Pre-Funded Warrants to remove the potential requirement that they could be settled in cash under certain circumstances. At December 31, 2022, the Pre-funded Warrants are recorded as equity, using their fair value as of the amendment date.

The fair value of the Common and Pre-Funded Warrants were estimated using the Black-Scholes option pricing model with the following assumptions:

Expected term (in years)	3.7
Volatility	91.53 %
Risk-free interest rate	4.11 %
Dividend yield	0.00 %

A summary of the Company's outstanding common stock warrants as of December 31, 2022 is as follows:

	Warrants
Outstanding as of December 31, 2021	125,618
Warrants granted and issued	40,000,000
Warrants exercised	(1,750,000)
Warrants exchanged	—
Outstanding as of December 31, 2022	38,375,618

10. LEASES

The following table summarizes our lease assets and liabilities as of December 31, 2022 and 2021:

		Operating (in thousands)	
		December 31,	December 31,
ROU Assets and Liabilities	Balance Sheet Location	2022	2021
ROU - Asset	Right-of-use assets	$ 857	$ 1,298
Lease liabilities (current)	Operating lease liabilities, current	477	442
Lease liabilities (non-current)	Operating lease liabilities, non-current	414	891

The following table summarizes our lease related costs for the twelve months ended December 31, 2022 and 2021:

		Operating *(in thousands)*	
Lease Cost	**Statement of Operations Location**	**2022**	**2021**
Operating Lease Cost	General and administrative	$ 489	$ 505
Total Lease Cost		$ 489	$ 505

Average lease terms and discount rates for the Company's operating leases were as follows:

Other Information	**Year Ended December 31, 2022**	**December 31, 2021**
Weighted-average remaining lease term		
Operating leases	1.8 years	2.8 years
Weighted-average discount rate		
Operating leases	5.69%	5.69%

The following table summarizes the maturities of lease liabilities as of December 31, 2022:

Year	**Operating** *(in thousands)*
2023	$ 515
2024	425
Thereafter	—
Total lease payments	940
Less: interest	49
Total lease liabilities	$ 891

11. INCOME TAXES

The Company's current tax provision for the years ended December 31, 2022 and 2021 is $0 and $0, respectively. The Company's deferred tax provision for the years ended December 31, 2022 and 2021 is $0 and $0, respectively.

A reconciliation of the Company's deferred taxes is as follows (in thousands):

	Year ended December 31,	
	2022	2021
Deferred Tax Assets		
Operating Lease Liability	$ 282	$ 420
Stock-based compensation	8,131	6,606
License fee	554	594
Net operating loss carryforwards	88,090	79,429
Research and development tax credits	21,397	14,940
Capitalized R&D expense	14,910	—
Other	1,085	1,352
Total Deferred Tax Assets	$ 134,449	$ 103,341
Valuation Allowance	$ (134,177)	$ (102,932)
Net Deferred Tax Assets	$ 272	$ 409
Deferred Tax Liabilities		
Right of Use Asset	(272)	(409)
Net Deferred Tax Liabilities	$ (272)	$ (409)
Net deferred tax asset (liability)	$ —	$ —

Deferred tax assets result primarily from unutilized net operating losses, research tax credits, stock-based compensation, operating lease liability, and timing differences as a result of the Company reporting its income tax returns. As of December 31, 2022, the Company had approximately $280.6 million of federal operating losses (“NOLs”) carried forward. Of this amount, approximately $3.3 million will begin to expire in 2037 and approximately $277.3 million are carried forward indefinitely. The Company had approximately $572.8 million in state and city net operating loss carryforwards available to offset future taxable income.

As of December 31, 2022, the Company had federal research tax credits (R&D) of approximately $4.9 million which may be used to offset future tax liabilities. Additionally, the Company had a federal orphan drug credit (“ODC”) related to qualifying research of $16.5 million. These tax credit carryforwards will begin to expire at various times beginning in 2037 for federal purposes.

The NOL, R&D and ODC credits carry forwards are subject to review and possible adjustment by the U.S. and state tax authorities. NOL carry forwards and credit carry forwards may become subject to an annual limitation in the event of certain cumulative changes in the ownership interest of significant shareholders, as defined under Sections 382 and 383 Internal Revenue Code. This could limit the amount of NOLs and credits that the Company can utilize annually to offset future taxable income or tax liabilities. As of December 31, 2022, the Company has not performed such an analysis. Subsequent ownership changes and proposed future changes to tax rules in respect of the utilization of losses carried forward may further affect the limitation in future years.

In assessing the realizability of the Company’s deferred tax assets, management considers whether or not it is more likely than not that some portion or all of the deferred tax assets will not be realized. The ultimate realization of deferred tax assets is dependent upon the generation of future taxable income. The Company’s assessment is based on the weight of available evidence, including cumulative losses since inception and expected future losses and, as such, the Company does not believe it is more likely than not that the deferred tax assets will be realized. Accordingly, a full valuation allowance has been established and no deferred tax assets and related tax benefit have been recognized in the accompanying financial statements. At December 31, 2022 and 2021, the Company recorded valuation allowances of $134.2 million and $102.9 million, respectively. The increase in valuation allowance is primarily driven by additional net operating loss.

The Company files its income tax returns in the United States, New York State, New York City, California, Massachusetts, and New Jersey. All years remain subject to examination for federal and state purpose.

The U.S. federal statutory corporate tax rate reconciles to the Company's effective tax rate for the years ended December 31, 2022 and 2021:

	Year Ended December 31,	
	2022	2021
Federal statutory rate	21.0 %	21.0 %
State and local taxes net of federal tax benefit	10.2	10.7
Credits	7.8	5.6
Permanent Differences	(0.1)	0.5
Change in valuation allowance	(37.9)	(37.7)
Stock Compensation	(1.1)	—
Other	0.1	(0.1)
Total	0.0%	0.0 %

12. BENEFIT PLANS

The Company established a defined contribution savings plan under Section 401(k) of the Internal Revenue Code in 2018. This plan covers substantially all employees who meet minimum age and service requirements and allows participants to defer a portion of their annual compensation on a pre-tax basis. Matching contributions to the plan may be made at the discretion of the Company's Board. The Company made approximately $0.4 million and $0.2 million in matching contributions to the plan during the year ended December 31, 2022 and 2021, respectively.

13. NET LOSS PER COMMON SHARE

Basic net loss per common share is computed by dividing the net loss available to common stockholders by the weighted-average number of shares of common stock outstanding during the period.

Diluted net loss per common share is computed by giving the effect of all potential shares of common stock, including stock options, preferred shares, warrants and instruments convertible into common stock, to the extent dilutive. Basic and diluted net loss per common share was the same for the years ended December 2022 and 2021, as the inclusion of all potential common shares outstanding would have been anti-dilutive.

The following table sets forth the computation of basic and diluted net loss per common share (in thousands, except share and per share data):

	Years Ended December 31,	
(in thousands, except for share data)	2022	2021
Numerator:		
Net loss	$ (82,508)	$ (105,584)
Denominator:		
Weighted-average common stock outstanding	37,825,431	25,598,181
Net loss per share attributable to common stockholders - basic and diluted	$ (2.18)	$ (4.12)

The Company's potentially dilutive securities, which include restricted stock units, stock options and common warrants, have been excluded from the computation of diluted net loss per share as the effect would be to reduce the net loss per share. Therefore, the weighted-average number of common shares outstanding used to calculate both basic and diluted net loss per share attributable to common stockholders is the same. The Company excluded the following potential common shares, presented based on amounts outstanding at December 31, 2022 and 2021, from the

computation of diluted net loss per share attributable to common stockholders because including them would have had an anti-dilutive effect:

	As of December 31,	
	2022	2021
Options to purchase common stock	4,874,047	4,704,888
Restricted stock units	815,509	469,485
Warrants to purchase common stock	30,125,618	125,618

14. RELATED PARTIES

In December 2018, the Company entered into an agreement (the "LaunchLabs Agreement") with ARE-LaunchLabs NYC LLC ("Alexandria LaunchLabs"), a subsidiary of Alexandria Real Estate Equities, Inc. for use of specified premises within the Alexandria LaunchLabs space on a month-to-month basis. A member of the Company's board of directors is the founder and executive chairman of Alexandria Real Estate Equities, Inc. During the years ended December 31, 2022 and 2021, the Company made payments to Alexandria LaunchLabs of approximately $0.1 million and $0.1 million, respectively under the LaunchLabs Agreement, which was recognized in research and development expenses. As of December 31, 2022, there were no amounts due to Alexandria LaunchLabs under the LaunchLabs Agreement.

15. SUBSEQUENT EVENTS

On January 3, 2023, the "Company entered into an Exclusive License and Supply Agreement (the "Agreement") with Mercury Pharma Group Limited (trading as Advanz Pharma Holdings), a company organized and existing under the laws of England and Wales ("ADVANZ PHARMA"), a UK headquartered global pharmaceutical company with a strategic focus on specialty, hospital, and rare disease medicines in Europe. Pursuant to the Agreement, the Company granted ADVANZ PHARMA the exclusive right and license to commercialize drug products containing AT-007 (also known as govorestat), the Company's proprietary Aldose Reductase Inhibitor (ARI) (the "Licensed Product"), for use in treatment of sorbitol dehydrogenase deficiency ("SORD") and Galactosemia in humans (each, a "Licensed Indication") in the European Economic Area, Switzerland and the United Kingdom (the "Territory"). The Company also grants ADVANZ PHARMA a right of negotiation and "most-favored nation" rights with respect to acquiring the European commercialization rights for any additional indications for which the Licensed Product may be developed in the future (or any other products the Company may develop solely to the extent used for the Licensed Indications).

ADVANZ PHARMA is required to use commercially reasonable efforts to launch and commercialize the Licensed Products in the major markets in the Territory in each Licensed Indication following, and subject to, receipt of marketing authorization therein. Under the Agreement, ADVANZ PHARMA agrees to pay the Company (i) an upfront payment of EUR 10 million (approx. USD $10.7 million), and certain development milestone payments upon clinical trial completions and receipt of marketing authorization in the Territory, as well as certain commercial milestone payments, totaling EUR 134 million (approx. USD $142.2 million) in the aggregate, and (ii) royalties of 20% of net sales of the Licensed Product. Such royalty rate will be payable on a country-by-country basis until the later of (i) the expiration of the licensed patents covering the composition of matter of AT-007, or (ii) 10 years after the European Medicines Agency's grant of marketing authorization for the Licensed Product. The royalties are subject to certain deductions, including certain secondary finishing costs, certain step-in establishment costs and a portion of fees for any potential third party patent licenses if applicable in the future. Following the initial term of the license, as described above, the royalty rate shall be reduced to 10% and shall continue in perpetuity unless the Agreement is terminated in various circumstances in accordance with its terms.

Certain of the patents licensed to ADVANZ PHARMA under the Agreement are sub-licensed from the University of Miami and Columbia University, and thus remain subject to certain obligations of the Company (including royalty obligations) to such institutions.

Under the Agreement, the Company remains responsible for development of the Licensed Product, and must conduct such development through grant of marketing authorizations in the Licensed Indications in the Territory and as otherwise required under such marketing authorization, in accordance with any timeframe required by regulatory authorities. The Company retains sole responsibility for the conduct of all clinical trials (subject in some circumstances to cost-sharing with ADVANZ PHARMA), unless the Company provides ADVANZ PHARMA prior consent to conduct certain studies following marketing authorization, or ADVANZ PHARMA exercises certain step-in rights (as described below). The Company also agrees to manufacture and supply the Licensed Product in bulk form to ADVANZ PHARMA. ADVANZ PHARMA is responsible for secondary packaging and release for the Territory.

The Agreement includes indemnification obligations on the part of both parties for third-party claims arising out of, among other things, a breach of the Agreement; an election by the other party not to initiate a recall; gross negligence or willful misconduct; and violation of applicable laws. In addition, both parties have agreed to indemnification obligations for third party liability product liability claims and certain exclusions from liability disclaimers, such as for breaches of confidentiality, death or personal injury caused by negligence or willful default.

In certain circumstances, including in the event of specified supply shortages, bankruptcy and certain other financial events, a force majeure event lasting more than three months, or termination as a result of the Company's gross negligence or willful misconduct, ADVANZ PHARMA may exercise certain step-in rights. Such step-in rights include the ability for ADVANZ PHARMA to perform its own supply arrangements, and in some cases, specified development rights in the Licensed Indications in the Territory and assignment of certain contract rights. In all such circumstances, ADVANZ PHARMA must continue to pay royalties and milestone payments. ADVANZ PHARMA may recoup certain of its manufacturing and development establishment costs, and deduct such costs from royalties.

The Company may terminate the Agreement upon certain specified events, including ADVANZ PHARMA's failure to launch or achieve certain sales threshold for the Licensed Product in major markets within a certain timeframe, or if ADVANZ PHARMA challenges a licensed patent, and either party may terminate the Agreement upon the other party's material breach or insolvency, certain material safety issues or a force majeure event of the other party lasting longer than six months. ADVANZ PHARMA may also terminate the agreement if the Licensed Product does not receive marketing authorization for use in a Licensed Indication in any country in the Territory by a specified date, or in the event of the Company's gross negligence or willful misconduct (subject to a cure period).

ITEM 9. CHANGES IN AND DISAGREEMENTS WITH ACCOUNTANTS ON ACCOUNTING AND FINANCIAL DISCLOSURE.

None.

ITEM 9A. CONTROLS AND PROCEDURES.

Evaluation of Controls and Procedures

As of December 31, 2022, our management, with the participation of our Chief Executive Officer and our Interim Principal Financial Officer, evaluated the effectiveness of our disclosure controls and procedures as defined in Rules 13a-15(e) and 15d-15(e) of the Exchange Act. Disclosure controls and procedures include, without limitation, controls and procedures designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act is accumulated and communicated to management, including our principal executive and principal financial officers, as appropriate to allow timely decisions regarding required disclosure.

Management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving their objectives, and management necessarily applies its judgment in evaluating the cost-benefit relationship of possible controls and procedures. Based on this evaluation, our Chief Executive Officer and Interim Principal Financial Officer concluded that, as of December 31, 2022, the design and operation of our disclosure controls and procedures were effective at the reasonable assurance level.

Management's Annual Report on Internal Control over Financial Reporting

Management of the Company is responsible for establishing and maintaining adequate internal control over financial reporting as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act. Our internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

Management conducted an evaluation of the effectiveness of our internal control over financial reporting as of December 31, 2022 based on the framework in Internal Control-Integrated Framework (2013) issued by the Committee of Sponsoring Organizations of the Treadway Commission (COSO). Based on that evaluation, management has concluded that the Company's internal control over financial reporting was effective as of December 31, 2022.

Changes in Internal Control over Financial Reporting

There was no change in our internal control over financial reporting identified in connection with the evaluation required by Rule 13a-15(d) and 15d-15(d) of the Exchange Act that occurred during the fourth quarter of 2022 that has materially affected, or is 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.

Not Applicable.

PART III

ITEM 10. DIRECTORS, EXECUTIVE OFFICERS AND CORPORATE GOVERNANCE.

The information required by Item 10 is incorporated by reference to the information that will be contained in our 2023 Proxy Statement under the captions “Proposal 1 - Election of Directors,” “Principal Stockholders,” “Proposal 2 – Ratification of Independent Registered Public Accounting Firm” and “Audit Committee Report.”

ITEM 11. EXECUTIVE AND DIRECTOR COMPENSATION.

The information required by Item 11 is incorporated by reference to the information that will be contained in our 2023 Proxy Statement under the captions “Executive and Director Compensation,” “Compensation Discussion and Analysis,” “Compensation Committee Report,” “Compensation Committee Interlocks and Insider Participation,” “Compensation of Named Executives,” “Summary Compensation Table,” “Equity Incentive Plans,” “Non-Employee Director Compensation,” “Stock Option Grants,” “Outstanding Equity Awards at Fiscal Year-End,” “Health and Welfare Retirement Benefits,” and “Potential Payments and Benefits Upon Termination or Change-in-Control.”

ITEM 12. SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERS AND MANAGEMENT AND RELATED STOCKHOLDER MATTERS.

The information required by Item 12 is incorporated by reference to the information that will be contained in our 2023 Proxy Statement under the caption “Principal Stockholders.”

ITEM 13. CERTAIN RELATIONSHIPS AND RELATED TRANSACTIONS, AND DIRECTOR INDEPENDENCE.

The information required by Item 13 is incorporated by reference to the information that will be contained in our 2023 Proxy Statement under the caption “Certain Relationships and Transactions.”

ITEM 14. PRINCIPAL ACCOUNTANT FEES AND SERVICES.

The information required by Item 14 is incorporated by reference to the information that will be contained in our 2023 Proxy Statement under the caption “Independent Registered Public Accounting Firm”.

PART IV

ITEM 15. EXHIBITS, FINANCIAL STATEMENT SCHEDULES.

(a) The following documents are filed as part of this Annual Report

1. Financial Statements:

The following financial statements and schedules of the Registrant are contained in Part II, Item 8, "Financial Statements and Supplementary Data" of this Annual Report:

2. Financial Statement Schedules:

There are no Financial Statement Schedules included with this filing for the reason that they are not applicable or are not required or the information is included in the financial statements or notes thereto.

(b) Exhibits required by Item 601 of Regulation S-K

The information required by this Item is set forth on the exhibit index that follows the signature page of this Annual Report.

EXHIBIT INDEX

Exhibit Number	Description	Form	File No.	Exhibit	Filing Date
3.1	Amended and Restated Certificate of Incorporation of the Registrant, as amended.				
3.2	Certificate of Amendment to Amended and Restated Certificate of Incorporation of the Registrant.	8-K	001-38898	3.1	October 28, 2022
3.3+	Amended and Restated Bylaws of the Registrant.				
4.1+	Registration Rights Agreement, dated November 7, 2019, by and among the Registrant and the Purchasers.	8-K	001-38898	10.2	November 12, 2019
4.2+	Form of Common Stock Certificate of the Registrant.	10-Q	001-38898	4.1	August 12, 2019
4.3+	Amended and Restated Investors' Rights Agreement, by and among the Registrant and certain of its stockholders, dated November 5, 2018.	S-1/A	333-230838	4.2	April 29, 2019
4.4+	Form of Warrant, issued to affiliates of Brookline Capital Markets, a division of CIM Securities, LLC on March 13, 2017.	S-1/A	333-230838	4.3	April 29, 2019
4.5+	Form of Warrant, issued to affiliates of Brookline Capital Markets, a division of CIM Securities, LLC on November 5, 2018.	S-1/A	333-230838	4.4	April 29, 2019
4.6+	Form of Warrant, issued to affiliates of Brookline Capital Markets, a division of CIM Securities, LLC on April 9, 2019.	S-1/A	333-230838	4.5	April 29, 2019
4.7+	Form of Pre-Funded Warrant to Purchase Common Stock	8-K	001-38898	4.1	June 27, 2022
4.8+	Form of Common Warrant to Purchase Common Stock	8-K	001-38898	4.2	June 27, 2022

4.9+		Description of securities registered under Section 12 of the Exchange Act.		10-K		001-38898		4.7		March 13, 2020
10.1*+		Forms of Indemnity Agreement by and between the Registrant and its directors and executive officers.		S-1/A		333-230838		10.1		April 29, 2019
10.2*+		2019 Equity Incentive Plan.		S-1/A		333-230838		10.2		April 29, 2019
10.3*+		Forms of Option Grant Notice and Option Agreement under 2019 Equity Incentive Plan.		S-1/A		333-230838		10.3		April 29, 2019
10.4*+		Form of Restricted Stock Unit Grant Notice and Unit Award Agreement under 2019 Equity Incentive Plan.		S-1/A		333-230838		10.4		April 29, 2019
10.5*+		2016 Equity Incentive Plan, as amended.		S-1/A		333-230838		10.5		April 29, 2019
10.6*+		Forms of Stock Option Agreement under the 2016 Equity Incentive Plan, as amended.		S-1/A		333-230838		10.6		April 29, 2019
10.7*+		2019 Employee Stock Purchase Plan		S-1/A		333-230838		10.7		April 29, 2019
10.8†+		Exclusive License Agreement by and between the Registrant and The Trustees of Columbia University in the City of New York, dated October 26, 2016.		S-1		333-230838		10.11		April 12, 2019
10.9†		Exclusive License Agreement by and between the Registrant and Mercury Pharma Group Limited, dated January 3, 2023.								
10.10*+		Employment Agreement, by and between the Registrant and Riccardo Perfetti, dated August 28, 2019.		10-Q		001-38898		10.1		November 13, 2019
10.11*		Employment Agreement, by and between the Registrant and Shoshana Shendelman, dated March 9, 2020.		10-K		001-38898		10.13		March 13, 2020

10.12*		Amendment to Employment Agreement, by and between the Registrant and Riccardo Perfetti, dated March 9, 2020.		10-K		001-38898		10.14		March 13, 2020
10.13*		Offer Letter, by and between Steven Ortega and the Registrant, dated February 1, 2021.		10-K		001-38898		10.15		March 10, 2022
23.1		Consent of Ernst & Young LLP, an Independent Registered Public Accounting Firm.								
31.1		Rule 13a-14(a)/15d-14(a) Certification under the Exchange Act by Shoshana Shendelman, President and Chief Executive Officer (Principal Executive Officer).								
31.2		Rule 13a-14(a)/15d-14(a) Certification under the Exchange Act by Steven Ortega, Chief Accounting Officer (Interim Principal Financial Officer).								
32.1		Certification of Chief Executive Officer pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002 Section 1350 Certifications.								
32.2		Certification of Interim Principal Financial Officer pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002 Section 1350 Certifications.								
101.INS		Inline XBRL Instance Document.								
101.SCH		XBRL Taxonomy Extension Schema Document.								
101.CAL		XBRL Taxonomy Extension Calculation Linkbase Document.								
101.DEF		XBRL Taxonomy Extensions Definition Linkbase Document.								

101.LAB		XBRL Taxonomy Extension Label Linkbase Document.								
101.PRE		XBRL Taxonomy Extension Presentation Linkbase Document.								
104		Cover Page Interactive Data File (formatted as Inline XBRL with applicable taxonomy extension information contained in Exhibits 101).								

* Indicates a management contract or compensatory plan.
† Portions of this exhibit have been omitted.
+ Previously filed.

ITEM 16. 10-K SUMMARY

None.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the Company has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

Applied Therapeutics, Inc.

Dated: March 23, 2023

/s/ *Shoshana Shendelman*
Name: Shoshana Shendelman, Ph.D.
Title: President and Chief Executive Officer

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed below by the following persons on behalf of the Company and in the capacities indicated on the 23rd of March 2023.

Name	Title	Date
/s/ Shoshana Shendelman Shoshana Shendelman, Ph.D.	Chair of the Board President and Chief Executive Officer (Principal Executive Officer)	March 23, 2023
/s/ Steven Ortega Steven Ortega	Chief Accounting Officer (Principal Accounting Officer and Interim Principal Financial Officer)	March 23, 2023
/s/ Les Funtleyder Les Funtleyder	Director	March 23, 2023
/s/ Teena Lerner Teena Lerner, Ph.D.	Director	March 23, 2023
/s/ Stacy Kanter Stacy Kanter	Director	March 23, 2023
/s/ Joel S. Marcus Joel S. Marcus	Director	March 23, 2023
/s/ Jay S. Skyler Jay S. Skyler, M.D., MACP	Director	March 23, 2023

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