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, 2021

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 001-39279

Ayala Pharmaceuticals, Inc.

(Exact name of Registrant as specified in its Charter)

Delaware	**82-3578375**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. Employer Identification No.)**
Oppenheimer 4 Rehovot, Israel	**7670104**
(Address of principal executive offices)	**(Zip Code)**

(857) 444-0553
(Registrant's telephone number, including area code)

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, $0.01 par value per share	**AYLA**	**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, 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. ☐

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

The aggregate market value of the voting and non-voting common equity held by non-affiliates of the registrant, based on the closing price of the shares of common stock on The Nasdaq Stock Market on June 30, 2021 was approximately $46.0 million.

The number of shares of Registrant's Common Stock outstanding as of March 15, 2022 was 14,080,383.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's definitive Proxy Statement, relating to its 2022 Annual Meeting of Stockholders to be filed with the Securities and Exchange Commission are incorporated by reference into Part III of this Annual Report on Form 10-K.

Table of Contents

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K contains forward-looking statements. We intend such forward-looking statements to be covered by the safe harbor provisions for forward-looking statements contained in Section 27A of the Securities Act of 1933, as amended, or the Securities Act, and Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act. All statements other than statements of historical facts contained in this Annual Report, including without limitation statements relating to our development of AL101 and AL102, our ability to continue as a going concern, our future capital needs and our need to raise additional funds, the promise and potential impact of our preclinical or clinical trial data, the timing of and plans to initiate additional clinical trials of AL101 and AL102, the timing and results of any clinical trials or readouts, and the anticipated impact of COVID-19 on our business, are forward-looking statements. These statements involve known and unknown risks, uncertainties and other important factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements.

In some cases, you can identify forward-looking statements by terms such as “may,” “will,” “should,” “expect,” “plan,” “anticipate,” “could,” “intend,” “target,” “project,” “contemplate,” “believe,” “estimate,” “predict,” “potential”, or “continue” or the negative of these terms or other similar expressions, although not all forward-looking statements are identified by these terms or expressions. The forward-looking statements in this Annual Report are only predictions. 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 business, financial condition and results of operations. These forward-looking statements speak only as of the date of this Annual Report and are subject to a number of important factors that could cause actual results to differ materially from those in the forward-looking statements, including the factors described under the sections in this Annual Report titled “Risk Factors” and “Management’s Discussion and Analysis of Financial Condition and Results of Operations.”

Moreover, we operate in an evolving environment. New risk factors and uncertainties may emerge from time to time, and it is not possible for management to predict all risk factors and uncertainties.

You should read this Annual Report and the documents that we reference in this Annual Report completely and with the understanding that our actual future results may be materially different from what we expect. We qualify all of our forward-looking statements by these cautionary statements. Except as required by applicable law, we do not plan to publicly update or revise any forward-looking statements contained herein, whether as a result of any new information, future events, changed circumstances or otherwise.

SUMMARY RISK FACTORS

Our business is subject to numerous risks and uncertainties, including those described in Part II Item 1A. “Risk Factors” in this Annual Report on Form 10-K. You should carefully consider these risks and uncertainties when investing in our ordinary shares. The principal risks and uncertainties affecting our business include the following:

- We have incurred significant losses since inception and anticipate that we will continue to incur losses for the foreseeable future. We are not currently profitable, and we may never achieve or sustain profitability;
- We will require additional capital to fund our operations, and if we fail to obtain necessary financing, we may not be able to complete the development and commercialization of AL101 and AL102;
- Our recurring losses from operations raise substantial doubt regarding our ability to continue as a going concern;
- We have a limited operating history and no history of commercializing pharmaceutical products, which may make it difficult to evaluate the prospects for our future viability;
- We are heavily dependent on the success of AL101 and AL102, our most advanced product candidates, which are still under clinical development, and if either AL101 or AL102 does not receive regulatory approval or is not successfully commercialized, our business may be harmed;
- Due to our limited resources and access to capital, we must prioritize development of certain programs and product candidates; these decisions may prove to be wrong and may adversely affect our business;
- The outbreak of COVID-19, may adversely affect our business, including our clinical trials;
- Our ability to use our net operating loss carryforwards to offset future taxable income may be subject to certain limitations;
- Our product candidates are designed for patients with genetically defined cancers, which is a rapidly evolving area of science, and the approach we are taking to discover and develop product candidates is novel and may never lead to marketable products;
- We were not involved in the early development of our lead product candidates; therefore, we are dependent on third parties having accurately generated, collected and interpreted data from certain preclinical studies and clinical trials for our product candidates;
- Enrollment and retention of patients in clinical trials is an expensive and time-consuming process and could be made more difficult or rendered impossible by multiple factors outside our control;
- If we do not achieve our projected development and commercialization goals in the timeframes we announce and expect, the commercialization of our product candidates may be delayed and our business will be harmed.
- Our product candidates may cause serious adverse events or undesirable side effects, which may delay or prevent marketing approval, or, if approved, require them to be taken off the market, require them to include safety warnings or otherwise limit their sales;
- The market opportunities for AL101 and AL102, if approved, may be smaller than we anticipate;
- We may not be successful in developing, or collaborating with others to develop, diagnostic tests to identify patients with Notch-activating mutations;
- We have never obtained marketing approval for a product candidate and we may be unable to obtain, or may be delayed in obtaining, marketing approval for any of our product candidates;

- Even if we obtain approval from the U.S. Food and Drug Administration, or FDA, for our product candidates in the United States, we may never obtain approval for or commercialize them in any other jurisdiction, which would limit our ability to realize their full market potential;

- We have been granted Orphan Drug Designation for AL101 for the treatment of ACC and may seek Orphan Drug Designation for other indications or product candidates, and we may be unable to maintain the benefits associated with Orphan Drug Designation, including the potential for market exclusivity, and may not receive Orphan Drug Designation for other indications or for our other product candidates.

- Although we have received fast track designation for AL101, and may seek fast track designation for our other product candidates, such designations may not actually lead to a faster development timeline, regulatory review or approval process.

- We face significant competition from other biotechnology and pharmaceutical companies and our operating results will suffer if we fail to compete effectively;

- We are dependent on a small number of suppliers for some of the materials used to manufacture our product candidates, and on one company for the manufacture of the active pharmaceutical ingredient for each of our product candidates;

- Our existing collaboration with Novartis is, and any future collaborations will be, important to our business. If we are unable to maintain our existing collaboration or enter into new collaborations, or if these collaborations are not successful, our business could be adversely affected;

- Enacted and future healthcare legislation may increase the difficulty and cost for us to obtain marketing approval of and commercialize our product candidates, if approved, and may affect the prices we may set;

- If we are unable to obtain, maintain, protect and enforce patent and other intellectual property protection for our technology and products or if the scope of the patent or other intellectual property protection obtained is not sufficiently broad, our competitors could develop and commercialize products and technology similar or identical to ours, and we may not be able to compete effectively in our markets;

- We may engage in acquisitions or in-licensing transactions that could disrupt our business, cause dilution to our stockholders or reduce our financial resources; and

- Risks related to our operations in Israel could materially adversely impact our business, financial condition and results of operations.

PART I

Item 1. Business.

Overview

We are a clinical-stage oncology company focused on developing and commercializing small molecule therapeutics for patients suffering from rare and aggressive cancers. Our differentiated development approach is predicated on identifying and addressing tumorigenic drivers of cancer, through a combination of our bioinformatics platform and next-generation sequencing to deliver targeted therapies to underserved patient populations. Our current portfolio of product candidates, AL101 and AL102, targets the aberrant activation of the Notch pathway using gamma secretase inhibitors. Gamma secretase is the enzyme responsible for Notch activation and, when inhibited, turns off the Notch pathway activation. Aberrant activation of the Notch pathway has long been implicated in multiple solid tumor and hematological cancers and has often been associated with more aggressive cancers. In cancers, Notch is known to serve as a critical facilitator in processes such as cellular proliferation, survival, migration, invasion, drug resistance and metastatic spread, all of which contribute to a poorer patient prognosis. AL101 and AL102 are designed to address the underlying key drivers of tumor growth, and our initial Phase 2 clinical data of AL101 suggest that our approach may address shortcomings of existing treatment options. We believe that our novel product candidates, if approved, have the potential to transform treatment outcomes for patients suffering from rare and aggressive cancers.

Our product candidates, AL101 and AL102, are being developed as potent, selective, small molecule gamma secretase inhibitors, or GSIs. We obtained an exclusive, worldwide license to develop and commercialize AL101 and AL102 from Bristol-Myers Squibb Company, or BMS, in November 2017. BMS evaluated AL101 in three Phase 1 studies involving more than 200 total subjects and AL102 in a single Phase 1 study involving 36 subjects with various cancers who had not been prospectively characterized for Notch activation, and to whom we refer to as unselected subjects. While these Phase 1 studies did not report statistically significant overall results, clinical activity was observed across these studies in cancers in which Notch has been implicated as a tumorigenic driver.

AL102, is being developed as oral GSI for the treatment of desmoid tumors, for which the FDA has agreed, based on data from AL101 and AL102 Phase 1 studies including durable responses observed in patients with desmoid tumors, to proceed with a Phase 2/3 pivotal study, which can potentially be used as a registrational study.

mid-2022 with part B of the study to commence immediately thereafter. Part B of the study will be a double-blind placebo-controlled study enrolling up to 156 patients with progressive disease, randomized between AL102 or placebo. The study’s primary endpoint will be progression free survival, or PFS with secondary endpoints including ORR, duration of response, or DOR and patient reported Quality of Life, or QOL measures.

Desmoid tumors are rare, disfiguring and often debilitating types of soft tissue tumors. Desmoid tumors have an annual incidence of approximately 1,700 patients in the United States. There are currently no therapies approved by the U.S. Food and Drug Administration or FDA for patients with desmoid tumors. Given the slowly progressive nature of the disease, we believe these patients will be best served by an oral therapy. BMS conducted a Phase 1 study of AL102 in 36 subjects with heavily pretreated unselected solid tumors. While this Phase 1 study did not report statistically significant overall results, the study included one subject with desmoid tumors who was observed to have SD for over six months. In a separate Phase 1 study of AL101, three Desmoid subjects were included, and two of these subjects had partial responses and have continued treatment in a post-trial expanded access protocol, and both maintained their responses, and one subject had stable disease. These results were published in Current Oncology in September 2021. We believe that GSIs have the potential to treat patients with desmoid tumors based on the data we have obtained to date.

The pivotal Phase 2/3 RINGSIDE trial is designed to evaluate the efficacy, safety and tolerability of AL102 in adult and adolescent patients with desmoid tumors. Part A of the study is an open-label and completed the enrollment of 36 patients with progressive desmoid tumors in three study arms across three doses of AL102: 1.2 mg daily, or QD, 2 mg twice weekly, or QIW, and 4 mg twice weekly, or QIW with initial follow up of safety, tolerability and tumor volume by MRI after 16 weeks in order to determine the optimal dose. At the end of Part A, all patients will be eligible to enroll into an open label extension study at the selected dose where long-term efficacy and safety will be monitored. The effect on absorption of AL102 is also being evaluated in Part A.

We are also developing AL102 for the treatment of other rare indications including T-ALL, an aggressive, rare form of T-cell specific leukemia. T-ALL has an annual incidence of approximately 1,200 patients in the United States, of which an estimated 400 patients, including pediatric patients, present for the treatment of relapsed/refractory, or R/R, T-ALL. Approximately 65% of all R/R T-ALL patients have Notch-activating mutations. In addition, there is an incremental subset of patients with Notch pathway activation who do not bear Notch-activating mutations. R/R T-ALL is characterized by chemotherapy resistance, induction failure and tendency for early relapse, as 55% of adult patients and 20% of pediatric patients will relapse following first-line therapy. In the Phase 1 study of AL101, which included 26 unselected, heavily pretreated evaluable T-ALL subjects treated with 4 mg or 6 mg dose levels, a CR was observed in two T-ALL subjects and a PR was observed in one T-ALL subject. Of the three T-ALL subjects who displayed a response, two had a confirmed Notch-activating mutation. Based on these findings and supporting data from our preclinical studies, we intend to commence a Phase 2 clinical trial of AL102 for the treatment of R/R T-ALL in the second half of 2022, subject to the impact of COVID-19 on our business.

We are collaborating with Novartis International Pharmaceutical Limited, or Novartis, to develop AL102 for the treatment of multiple myeloma, or MM, in combination with Novartis' B-cell maturation antigen, or BCMA, targeting therapies. We granted Novartis the exclusive ability to evaluate, develop and potentially license and commercialize AL102 exclusively as a monotherapy and in combination with other therapies for the treatment of MM. Novartis conducted a preclinical study evaluating AL102 alone and in combination with Novartis' bi-specific antibody. Using a cell line model of human MM, Novartis' study showed that treatment with AL102 resulted in an approximate 20-fold increase in the levels of cell surface expression of BCMA. Furthermore, using human MM cells from donors, Novartis' study showed that AL102 enhanced BCMA-CD3 bi-specific antibody redirected t-cell cytotoxicity activity in vitro. We believe that the clinical activity of BCMA-targeting agents may also be enhanced in clinical trials when used in combination with a GSI such as AL102. The first patient was dosed with AL102 in combination with Novartis' BCMA targeting agent in April 2021.

We are currently evaluating AL101 as a monotherapy in an open-label Phase 2 clinical trial for the treatment of recurrent/metastatic adenoid cystic carcinoma, or R/M ACC, for patients bearing Notch-activating mutations. We refer to this trial as the ACCURACY trial. We use next-generation sequencing, or NGS, to identify patients with Notch-activating mutations, an approach that we believe will enable us to target the patient population with cancers that we believe are most likely to respond to and benefit from AL101 treatment. We chose to initially target R/M ACC based on our differentiated approach, which is comprised of: data generated in a Phase 1 study of AL101 in unselected, heavily pretreated subjects conducted by BMS, our own data generated in patient-derived xenograft models, our bioinformatics platform and our expertise in the Notch pathway.

ACC is a rare malignancy of the secretory glands, most commonly of the salivary glands. It has an annual incidence of approximately 3,400 patients in the United States, approximately 1,700 of whom are R/M ACC patients. There are currently no FDA-approved therapies for patients with R/M ACC. Based on scientific literature and our bioinformatics research, we estimate that 18% to 22% of R/M ACC patients have Notch-activating mutations. These Notch patients have a significantly worse prognosis, with estimated overall median survival rates roughly four times shorter than patients without Notch-activating mutations. According to published data from 31 Phase 2 clinical trials in ACC conducted since 2005 using a variety of treatment modalities, these treatments showed limited or no clinical activity in unselected ACC subjects. The objective response rates, or ORR, in 30 of these trials, ranged from 0% to 20%, with a 47% ORR observed in one trial conducted in China. In 15 of the 31 trials, a 0% ORR was observed. ORR includes subjects who displayed either a complete response, or CR, or a partial response, or PR.

We are currently conducting our ongoing Phase 2 ACCURACY trial for the treatment of R/M ACC in subjects with progressive disease and Notch-activating mutations. Our interim data for the 4mg cohort of the ACCURACY trial are as of July 30, 2020, and include safety data from 45 subjects and efficacy data from 40 subjects as of the date of the first radiographic scan, AL101, which was generally well tolerated with manageable side effects, showed a 68% disease control rate (total subjects who displayed either a response or stable disease), with an unconfirmed 15% ORR. A confirmed response is a response observed in two or more scans, an unconfirmed response that may potentially be confirmed is a response observed in only one scan for a patient who remains on trial and an unconfirmed response that will remain unconfirmed is a response observed in only one scan for a patient who has left the trial. This unconfirmed 15% ORR included no CRs and six PRs (three confirmed PRs and three unconfirmed PRs that will remain unconfirmed) and 53% of subjects displaying stable disease, or SD.

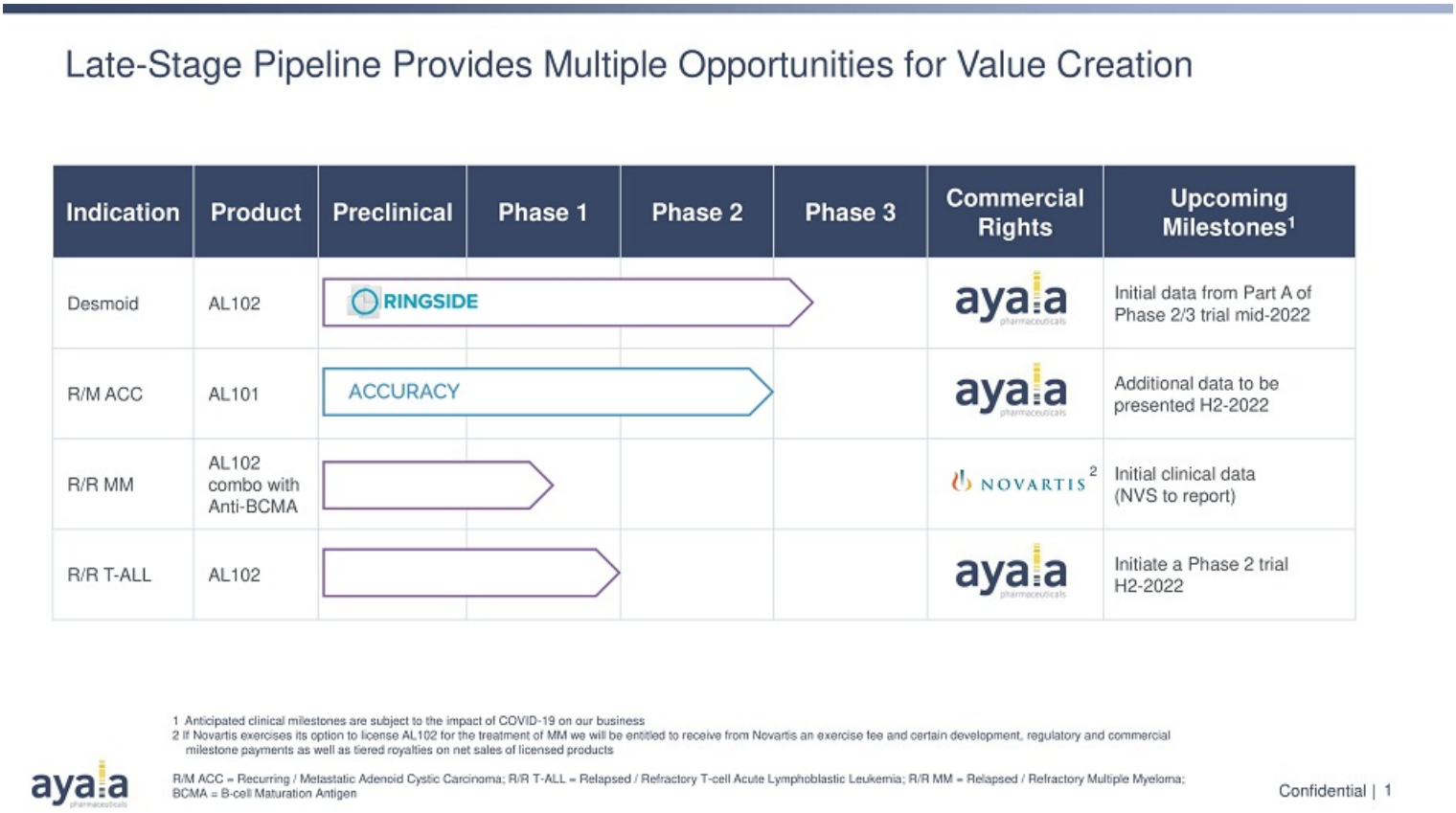
Interim data from the 6mg cohort as of July 9, 2021, including safety data from 42 subjects and efficacy data from 33 subjects as of the date of the first radiographic scan, showed that AL101, has been generally well tolerated with manageable side effects, and has demonstrated a 69.7% disease control rate, with an unconfirmed 9.1% ORR. This unconfirmed 9.1% ORR included no CRs and 3 PRs (two confirmed PRs and one unconfirmed PRs that will remain unconfirmed) and 60.6% of subjects displaying SD.

If approved, we believe that AL101 has the potential to become the first FDA-approved therapy for patients with R/M ACC and to address the unmet medical need of these patients. AL101 was granted Orphan Drug Designation for the treatment of ACC in May 2019 and fast track designation in February 2020 for the treatment of R/M ACC. In the second quarter of 2020, we commenced dosing of patients in our ACCURACY trial for the treatment of R/M ACC with Notch-activating mutations at the higher dose of 6 mg. We reported initial data from this trial in 2021 and plan to report additional data from this trial in the second half of 2022.

As part of our efforts to focus our resources on the more advanced programs and studies including the RINGSIDE study in desmoid tumors and the ACCURACY study for ACC, we elected to discontinue the TENACITY trial, which was evaluating AL101 as a monotherapy in an open-label Phase 2 clinical trial for the treatment of patients with Notch-activated R/M triple negative breast cancer, or TNBC.

Our product candidates have been or are being evaluated in clinical trials at leading oncology centers across the United States, including MD Anderson Cancer Center, Memorial Sloan Kettering Cancer Center and Massachusetts General Hospital, and in centers in Canada, Israel and Europe.

The following chart summarizes our current portfolio of product candidates:



Our History and Team

We were founded in November 2017 when we acquired an exclusive, worldwide license to AL101 (previously called BMS-906024) and AL102 (previously called BMS-986115), from BMS. We have assembled a team with extensive experience in building and operating clinical and commercial organizations, particularly in oncology and rare diseases. Our Chief Executive Officer, Roni Mamluk, Ph.D., has extensive experience in the biopharmaceutical industry and has led our business since its inception. Our Chief Medical Officer, Gary Gordon, M.D., Ph.D., is an oncologist with clinical research experience from John Hopkins School of Medicine and in oncology drug development roles at AbbVie, Inc. Dr. Gordon was involved in the development and commercialization plans for venetoclax, celecoxib and veliparib. Members of our management team have held leadership positions at companies that have successfully discovered, acquired, developed and commercialized therapies for a range of rare diseases and cancers, including Chiasma Inc., Adnexus Therapeutics, Inc., AbbVie Inc., Abbott Laboratories, Protalix Biotherapeutics, Inc. and Teva Pharmaceutical Industries Ltd.

Our Strategy

Our goal is to develop and commercialize therapies that improve treatment outcomes for patients with aggressive cancers. The key elements of our strategy are:

- ***Rapidly advance the clinical development of AL102 for the treatment of desmoid tumors.*** We are currently conducting our pivotal Phase 2/3 RINGSIDE study, which could potentially be used as a registrational study, and where we have completed enrollment for Part A, evaluating AL102 for the treatment of desmoid tumors. There are currently no FDA-approved therapies for patients with desmoid tumors. We also intend to evaluate other indications in which we believe AL102 could potentially deliver substantial benefits to patients.

- ***Rapidly advance the clinical development of AL101 for the treatment of R/M ACC.*** We are currently conducting our Phase 2 ACCURACY trial of AL101 for the treatment of R/M ACC. Our interim data from both the 4mg and 6mg dosing groups of our clinical trial showed encouraging initial signs of activity. We expect to report further results from this trial in a medical conference in the second half of 2022. AL101 was granted Orphan Drug Designation in May 2019 for the treatment of ACC and fast track designation in February 2020 for the treatment of R/M ACC. If approved, we believe that AL101 has the potential to become the first FDA-approved therapy for patients with R/M ACC. We may also seek regulatory approval of AL101 for the treatment of R/M ACC selectively in other territories.

- ***Advance the clinical development of AL102 for the treatment of R/R T-ALL.*** We are developing AL102 in additional indications with a high unmet medical need and in which Notch-activating mutations are known to be a tumorigenic driver, such as T-ALL and potentially in other hematological cancers. We intend to commence Phase 2 clinical trials of AL102 for the treatment of R/R T-ALL in the second half of 2022, subject to the impact of COVID-19 on our business. We also intend to evaluate other indications in which we believe AL102 could potentially deliver substantial benefits to patients.

- ***Collaborate with select diagnostic developers to identify and expand our addressable patient population.*** Consistent with our targeted approach to oncology, our development strategy is based on using companion diagnostics to identify and expand patient populations with Notch-activating mutations. Commercially available diagnostic tests are limited in their ability to test for all potential Notch-activating mutations. To address this, we have entered into a collaboration agreement with Tempus to use their assay to assist in patient selection in our clinical trials, and that is designed to detect across all four Notch genes and a wider range of Notch gene rearrangements than what is possible with commercially available diagnostic tests today.

- ***Commercialize our product candidates, if approved, to address the unmet medical need of underserved patient populations with rare and aggressive cancers.*** We intend to commercialize our product candidates, if approved, by building our own specialized sales and marketing organization initially in the United States. We believe our target market can be addressed by a small number of dedicated marketing and medical sales specialists covering specialized oncologists treating the target patient population. We may also selectively pursue strategic collaborations with third parties to maximize the commercial potential of our product candidates, if approved.

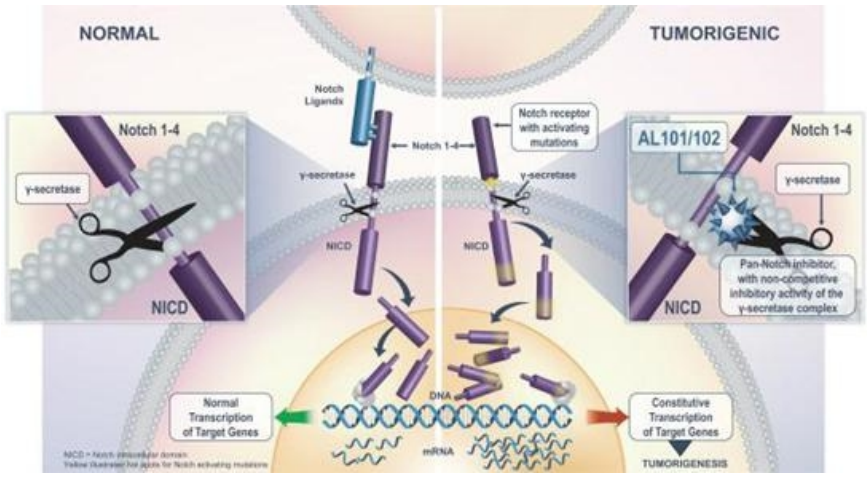
- ***Evaluate strategic collaborations to maximize the potential of our portfolio.*** We are continuously evaluating opportunities to expand our portfolio of product candidates through in-licensing, acquisition and other collaboration opportunities to jointly develop product candidates and maximize the value of our company. We have already established a collaboration with Novartis to develop AL102 in combination with Novartis' BCMA-targeting therapies for the treatment of MM and intend to assess other collaboration opportunities by leveraging our novel GSI technology.

Our Product Candidates

The Role of the Notch Pathway

The Notch pathway has long been implicated in multiple solid tumor and hematological cancers, and often has been associated with more aggressive cancers. Notch receptors serve as critical facilitators in processes such as cellular proliferation, survival, migration, invasion, drug resistance and metastatic spread, which all contribute to a poorer prognosis. Humans have four Notch receptors, known as Notch 1, 2, 3 and 4, as well as five transmembrane-bound ligands. Different forms of cancer are associated with different types of Notch mutations.

Normal and Tumorigenic Signaling of Notch



As seen on the left side of the above graphic, normal Notch receptor signaling is initiated by the binding of a ligand expressed on an adjacent cell, which triggers a conformational change, permitting cleavage of the Notch receptor by the g-secretase complex. As seen on the right side of the above graphic, this cleavage releases the Notch intracellular domain, or NICD, which then translocates to the cell nucleus, interacts with transcription complexes and promotes the transcription of downstream target genes that regulate critical cell functions. This pathway activation is terminated by the degradation of NICD. Activating mutations in the Notch receptor lead to accumulation of the NICD and hyper-activation of the pathway, resulting in excess NICD. Hyper-activation of the Notch pathway promotes cellular proliferation, survival, migration, invasion, drug resistance and metastatic spread, which are each hallmarks of cancer.

Our Potent and Selective Investigational Gamma Secretase Inhibitors

We are developing targeted therapies designed to address the underlying key drivers of tumor growth in patients where GSI inhibition of the Notch pathway may lead to clinical benefit. Our current portfolio of product candidates targets the aberrant activation of the Notch pathway with GSIs. Gamma secretase is the enzyme responsible for Notch activation and, when inhibited, blocks the expression of Notch gene targets by blocking the final cleavage step required for Notch activation, thereby "turning off" the aberrant activation of the Notch pathway. We have designed our GSIs to selectively inhibit all four Notch receptors.

Our Bioinformatics Platform

We have developed a proprietary bioinformatics platform to analyze NGS data and identify patients in whom Notch is a tumorigenic driver. We apply our big-data analysis capabilities to identify and confirm patients with Notch-activating mutations who are likely sensitive to GSIs.

The first step in our bioinformatics process is to gather evidence from literature and identify indications in which Notch is a known tumorigenic driver. We then confirm there are a requisite number of patients with Notch alterations in a specific indication using our proprietary database to integrate genetic information from thousands of unidentified patients. We couple these methods with our analysis of PDX models, which allow us to assess the sensitivity of the tumors *in vivo* with Notch-activating mutations, for certain indications.

Our bioinformatics platform includes:

- Our Ayala Cancer Omics Research Database, or ACORD, which is used to collate NGS data and integrate Notch-activating mutations from approximately 250,000 patients with over 400 different forms of cancer and harbors approximately 27,000 unique Notch alterations. We continue to expand ACORD by gaining access to additional sources of NGS data and scientific literature. We believe that we possess the largest database of Notch-activating mutations.

- Open source and proprietary algorithms integrated into a dedicated software platform, resulting in over 20 specialized data processing pipelines. These algorithms transform DNA and RNA sequences into searchable parameters, including which cancers harbor potential Notch-activating mutations. A systems biology approach is then applied to explore pathways involved in drug resistance and inform the design of our future clinical trial designs and to consider potential treatment combinations and responses to GSI.

Our scientists continue to utilize unique capabilities in bioinformatics and functional biology to create a Notch-focused patient identification engine that we believe will result in the discovery of additional patients with currently undetected Notch-activating mutations.

Expanding Our Addressable Patient Population

In addition to the well-known scientific literature supporting Notch's tumorigenic role in various forms of cancer, we are developing our bioinformatics platform to potentially discover additional genetic alterations not currently covered in commercially available genetic screening panels. Currently available NGS tests only cover certain areas of Notch genes on the DNA level, however, we believe that there is no single test that covers all four Notch genes on the DNA and RNA level. As a result, these tests are able to detect only a subset of the patients with Notch-activating mutations. In order to develop a diagnostic test that can detect the full breadth of Notch-activating mutations on both the DNA and RNA level, we plan to collaborate with leading diagnostics companies to improve the testing capabilities for Notch-activating mutations. For example, we have a collaboration agreement with Tempus to use their assays to assist with patient selection for our future clinical trials and detect a wider range of Notch gene rearrangements than commercially available NGS tests.

We estimate that there are up to 12,000 newly diagnosed patients annually across the United States, Europe and Japan who have Notch pathway activation in the indications that we are currently targeting.

Our Novel Approach: AL101 and AL102

Differentiated GSI for the Treatment of Rare Cancers

AL101 and AL102 are potent and selective small molecule GSIs designed to inhibit the aberrant activation of the Notch pathway. In preclinical studies and three Phase 1 studies conducted by BMS, tumor responses were observed in cancers we are initially targeting and where Notch is known to be an important tumorigenic driver. Our further investigation using PDX models provided additional evidence supporting our targeted patient population development approach.

In preclinical studies, both AL101 and AL102 inhibited all four Notch genes at low concentrations, when compared to other GSIs either currently or previously under development as illustrated in the below graphic.

Comparative Inhibitory Potency of Five GSIs in a Notch Luciferase Reporter Assay

Inhibition of Constitutive Notch Signaling: IC50 (nM)1

	AL101 (BMS-906024)	AL102 (BMS-986115)	Niro-gacestat[2] (PF-03084014)	RO-4929097[3]	MK-0752[4]
Notch1	1.6	6.1	13	3.8	354
Notch2	0.7	2.9	15	4.4	403
Notch3	3.4	8.1	17	22	955
Notch4	2.9	4.4	16	12	874

(1) Luciferase reporter-based assay, inhibition of constitutive Notch signaling.

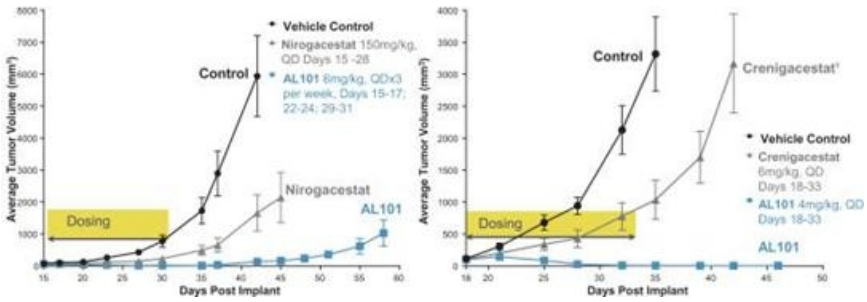
(2) Nirogacestat is being developed by SpringWorks Therapeutics, Inc.

(3) RO-4929097 was developed by F. Hoffmann-La Roche Ltd. and is not under active development.

(4) MK-0752 was developed by Merck & Co., Inc. and is not under active development.

The Notch cell-based transactivation assay was based on the ability of the released NICD to function as a transcription factor with other nuclear factors. Luciferase reporter activity provided a measure of the antagonism of Notch transcriptional activity. HeLa cervical cancer cells were transiently cotransfected with plasmids containing truncated Notch 1—4 receptors and a luciferase reporter vector. The cells were tested for Notch-activity in the absence or presence of GSIs at increasing concentrations. These data represent the GSI concentration inhibiting luciferase assay by 50%, or IC50. Lower concentrations correlate to more potent GSIs. As highlighted in the above graphic, AL101 and AL102 generally reached IC50 across all four Notch receptors at concentrations lower than other GSIs either currently or previously under development, which displayed the potency of AL101 and AL102 and supported the continued clinical development of these product candidates.

Effect on Tumor Growth in T-ALL Mouse Model



Tumor volume data are Mean ± SEM for 7-8 mice per treatment arm.

(1) Crenigacestat is being developed by Celgene Corporation, which was acquired by BMS.

Furthermore, as shown in the graphs above, AL101's stronger inhibition of tumor growth was observed in T-ALL mouse models when compared to other GSI molecules. We believe that AL101 and AL102, if approved, are GSIs with the potential to address the unmet medical need for patients with rare and aggressive tumors.

Our Novel Approach: AL102

Overview

AL102 is being developed as a potent, selective and oral GSI. We obtained an exclusive, worldwide license to develop and commercialize AL102 from BMS in November 2017. We are initially developing AL102 for the treatment of desmoid tumors. In addition, we are collaborating with Novartis to develop AL102 for the treatment of MM in combination with Novartis' BCMA-targeting agents.

The FDA has agreed, based on data from AL101 and AL102 studies including durable responses observed in patients with Desmoid tumors, to proceed with a Phase 2/3 pivotal study which can potentially be used as a registrational study. We recently completed enrollment in Part A and expect to report interim data by mid -2022, with Part B expected to commence immediately thereafter.

AL102 for the Treatment of Desmoid Tumors

Disease Background

Desmoid tumors, also called aggressive fibromatosis, are rare connective tissue neoplasms with an annual incidence of approximately 1,700 patients in the United States, and arise in the extremities, abdominal wall, mesenteric root, and chest wall. An estimated 7% to 15% of desmoid tumors present in the head and neck. They do not metastasize, but often aggressively infiltrate neurovascular structures and vital organs resulting in pain, loss of function, organ dysfunction, and death.

Desmoid tumors are typically diagnosed in patients between 15 and 60 years of age, more often in young adults, with a two- to three-fold female predominance and no significant racial or ethnic predilection.

Current Treatment Landscape

Although surgery and radiation remain the primary therapies for desmoid tumors, there are no treatment options for some patients given the diffuse nature of the tumor in some tissues. Surgery and radiation suffer from additional shortcomings including the morbidity associated with resection, disfigurement and/or functional impairment, post-operative complications and frequent recurrences. Aggressive adjuvant radiation therapy and surgical resection with wide margins of normal tissue may improve rates of post-surgical recurrence, which can occur in up to 72% of patients.

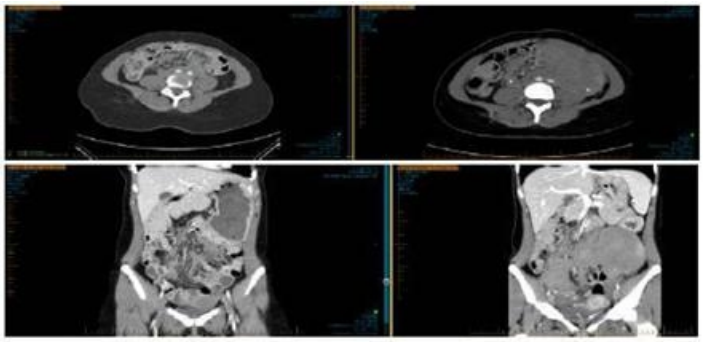
There are no FDA-approved systemic therapies for the treatment of unresectable, recurrent or progressive desmoid tumors and there is no currently accepted standard of care. Since current treatment responses are insufficient and not durable, there is an unmet medical need for the treatment of recurrent or progressive tumors (systemic therapy). Given the high recurrence and progression rates and lack of effective treatment options, we believe that there is a sizeable patient population with desmoid tumors with a high unmet medical need.

Clinical Evidence of GSI Activity in Desmoid Tumors

Based on data from multiple clinical evaluations, including data from three patients with desmoid tumors evaluated in a Phase 1 study of AL101 conducted by BMS, we believe that GSIs have the potential to address the shortcomings associated with existing treatment options for patients with desmoid tumors. In the Phase 1 study of AL101, PRs were observed in two subjects with desmoid tumors and SD was observed in another subject with desmoid tumors. In addition, three subjects, including two subjects from the Phase 1 study of AL101, entered into an expanded access program. Two case studies of adult patients with desmoid tumors treated with AL101 were published in *Current Oncology*.

The data included in the case studies were based on earlier Phase 1 results and compassionate use of AL101 in desmoid tumors. Both patients evaluated in these case studies, Case One and Case Two, presented with substantial tumor burden and symptomatic and life-threatening disease due to disease bulk and location. Both patients achieved long-lasting PRs with AL101 treatment with a maximum decrease in tumor size from baseline of 41% after approximately 1 year (55 weeks) of treatment in Case One, and a maximum decrease in tumor size from baseline of 60% after about 1.6 years (82 weeks) of treatment in Case Two. With continued monitoring, one patient was able to discontinue AL101 after 4.6 years of treatment, while maintaining a PR, and the other patient has maintained a PR at a reduced AL101 dose.

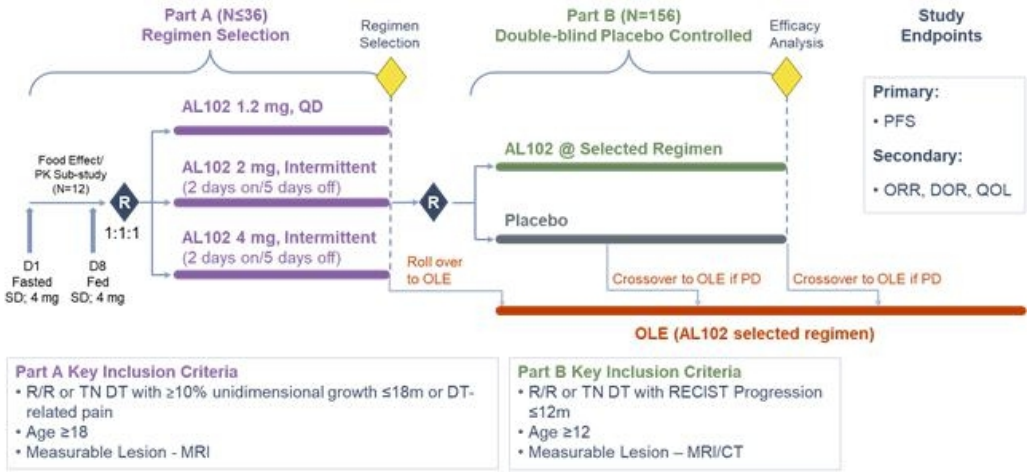
Below are scans from a patient who achieved a partial response and following the end of the BMS study opted to continue into an expanded access program



Phase 2/3 Pivotal Study of AL102

We are currently conducting our Phase 2/3 RINGSIDE pivotal study, which could potentially be used as a registrational trial, in adult and adolescent patients with desmoid tumors. The study's primary endpoint is progression free survival with secondary endpoints including, objective response rate, duration of response and patient reported Quality of Life measures. Part A of the study completed enrollment of 42 patients with progressive desmoid tumors in three study arms across three doses of AL102: 1.2 mg daily, 2 mg twice weekly, and 4 mg twice weekly with initial follow up to evaluate safety, tolerability and tumor volume by MRI after 16 weeks in order to determine the optimal dose. At the end of Part A, all patients will be eligible to enroll into an open label extension study at the selected dose where long-term efficacy and safety will be monitored. Part B of the study will start immediately after dose selection from Part A and will be a double-blind placebo-controlled study enrolling up to 156 patients with progressive disease, randomized between AL102 or placebo. We expect to report initial interim data read-out from Part A and dose selection around mid-2022, with Part B of the study to commence immediately thereafter.

The design of the pivotal phase 2/3 RINGSIDE study is below:

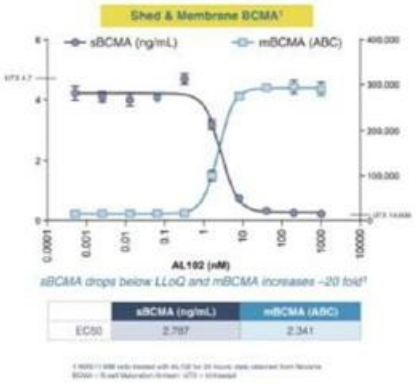


AL102 for the Treatment of Multiple Myeloma

Despite numerous advances in the treatment landscape for MM, the disease remains incurable. BCMA is ubiquitously expressed on myeloma cells and is currently a target of active studies utilizing a number of therapeutic approaches. Increasing the expression of the BCMA on target cells and reducing the shedding in the circulation is believed to potentially enhance therapies and increase responses.

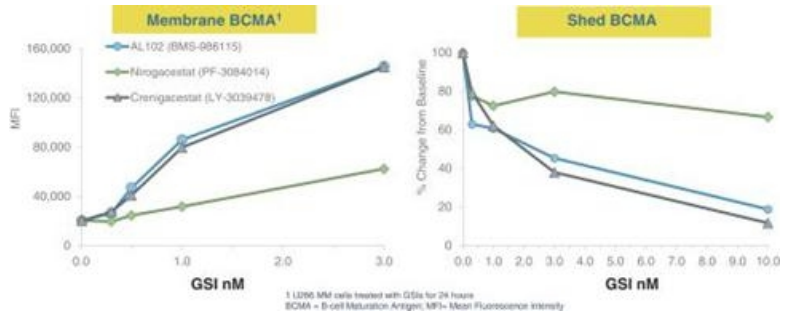
We are collaborating with Novartis to develop AL102 for the treatment of MM in combination with Novartis' BCMA-targeting therapies. In December 2018, we granted Novartis the exclusive ability to evaluate, develop and potentially license and commercialize AL102, as a monotherapy and in combination with other therapies, for the treatment of MM. Novartis conducted a preclinical study evaluating AL102 alone and in combination with an investigational anti-BCMA-CD3 bispecific antibody, or BisAb, controlled by Novartis. Using a preclinical cell line model of human multiple myeloma (KMS11) and shown in the figure below, Novartis' study showed that treatment with AL102 resulted in an approximate 20-fold increase in the levels of cell surface expression of BCMA and decreased shedding of BCMA to below lower levels of detection, as measured by levels of soluble BCMA.

AL102 Reduced Shed BCMA and Increased Membrane BCMA Levels in MM Cell Lines

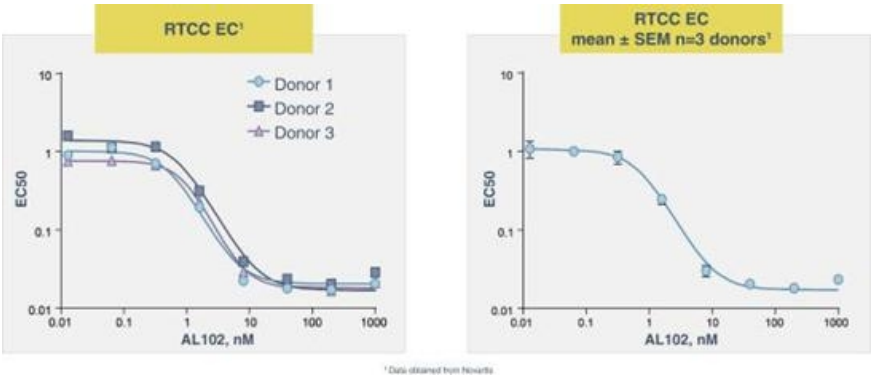


Soluble BCMA levels (ng/mL) from culture supernatants of KMS11 cells treated overnight with a serial dilution of AL102 are shown on the left Y axis. Antibody binding capacity, or ABC, of anti-BCMA on the surface of AL102 treated KMS11 cells is shown on the right Y axis. AL102 inhibited shedding of BCMA from KMS11 cells in a dose-dependent manner, which resulted in increased BCMA expression on the cell surface over the same dose range. Untreated KMS11 cells have a BCMA ABC of approximately 14,000. The average ABC with treatment of 10 nM AL102 was approximately 285,000, representing an approximate 20-fold increase in cell surface BCMA expression with AL102 treatment.

In addition, we tested increasing concentrations of three different GSI molecules, AL102, Nirogacestat and Crenigacestat on shed BCMA and membrane BCMA in UM266 multiple myeloma cell lines. As seen in the figures below, similar dose related activity as measured by mean flurescence intensity, or MFI, for membrane BCMA and by change from baseline for shed BCMA was observed for AL102 and Crenigacestat while relatively weaker activity was observed for Nirogacestat.



As shown below, in an assay designed by Novartis to evaluate the BisAb redirected t-cell cytotoxicity, or RTCC, activity *in vitro*, using human MM cells from donors, AL102 enhanced BisAb RTCC activity in a dose-dependent manner with enhancement of BisAb potency at concentrations of approximately 8nM or higher.



Novartis has initiated a Phase 1 study with its bi-specific anti-BCMA agent, and is responsible for the conduct and expenses of any trials of AL102 in combination with their BCMA-targeting agents. The first patient was dosed with AL102 in combination with Novartis' BCMA targeting agent in April 2021. We believe that the clinical activity of BCMA-targeting agents may also be enhanced in clinical trials when used in combination with a GSI such as AL102.

Al102 for the Treatment of T-cell Acute Lymphoblastic Leukemia

Disease Background

T-ALL is an aggressive, rare form of acute lymphoblastic leukemia, a disease which has an annual incidence of approximately 6,000 patients in the United States. T-ALL has an annual incidence of approximately 1,200 patients in the United States, of which an estimated 400, including pediatric patients, present for the treatment of R/R T-ALL. Notch is known to be a critical component of T-cell development and is inherently implicated as a tumorigenic driver in T-ALL. Approximately 65% of all T-ALL patients have Notch-activating mutations. In addition, there is an incremental subset of patients with Notch pathway activation who do not bear Notch-activating mutations.

T-ALL often presents as a result of the bone marrow being unable to produce sufficient amounts of normal blood cells, leading to symptoms such as anemia, infection, bleeding, bruising, fever, weakness and fatigue. Patients suffering from T-ALL frequently have central nervous system complications, as well as swollen lymph nodes in the mediastinum, or middle of the chest, which often affects breathing and circulation.

Current Treatment Landscape

The curative therapy for T-ALL is an allogeneic transplant. However, in order to be eligible to receive a transplant, patients must have exhibited a CR to prior therapies. The current standard first-line therapy for T-ALL is an intensive chemotherapy regimen, which yields overall survival rates greater than 80% among pediatric patients and approximately 50% among adult patients. Although first-line therapy is effective in most T-ALL patients, an estimated 55% of adult patients and 20% of pediatric patients will relapse. Second-line therapies for R/R T-ALL include targeted therapies administered in combination with chemotherapy and have shown limited efficacy, with an overall survival rate lower than 20% for pediatric patients. As a result, we believe that there remains a lack of effective treatment options for patients with R/R T-ALL.

Our Proposed Solution for R/R T-ALL: AL102

We are developing AL102 for the treatment of R/R T-ALL to address the lack of effective treatment options for these patients. In the Phase 1 study of AL101, which included 26 unselected, heavily pretreated T-ALL evaluable subjects treated at 4 mg or 6 mg dose levels, CRs were observed in two subjects and a PR was observed in one subject. Of the three subjects who displayed a response, two had a confirmed Notch-activating mutation. Based on these findings and preclinical studies, we intend to commence a Phase 2 clinical trial of AL102 for the treatment of R/R T-ALL in the second half of 2022, subject to the impact of COVID-19 on our business.

Phase 1 Study of AL102

Prior to our in-licensing of AL102, BMS conducted preclinical toxicity, PK and PD studies. AL102 was administered orally as a monotherapy in a Phase 1 study in 36 heavily pretreated cancer subjects. The primary objective of the study was to evaluate the safety, tolerability and proper dosage of AL102. Secondary objectives included evaluating the PK, PD changes in the expression of Notch-induced genes and the anti-tumor activity of

AL102. Formal statistical testing for these endpoints was not performed and the results were presented as descriptive statistics. The study had two arms. Arm A was designed to study daily dosing while Arm B was designed to study dosing two consecutive days each week. The design of this study, including dose groupings, is depicted below:

Dose escalation phase (n=36)

Of the 36 subjects evaluated in the study, SD was observed in 11 subjects, five of whom received AL102 for five months or longer and included subjects with ACC, fibromatosis (which is closely related to desmoid tumors), renal cell cancer and retroperitoneal fibroscarcoma.

The maximum tolerated dose for a once daily dosing regimen of Arm A was 1.5 mg, with one dose-limiting toxicity of Grade 3 nausea in the six dose-limited toxicity evaluable subjects. On the once daily schedule, the 2 mg dose was not tolerated, with dose-limiting toxicities in three of the five dose-limiting toxicity evaluable subjects, which included Grade 3 events of ileus, nausea, or pruritus/urticaria. A maximum tolerated dose was not established for a twice weekly dosing regimen of AL102, as Arm B was ongoing at the time that this study was terminated. The highest tolerated dose was 4 mg twice weekly, with no dose-limiting toxicities in the two dose-limiting toxicity evaluable subjects. A higher dose of 8 mg was not tolerated, with dose-limiting toxicities in two of the six dose-limiting toxicity evaluable subjects, which included Grade 3 diarrhea or Grade 3 nausea/dehydration/anorexia with Grade 2 fatigue. The most common TRAEs in this study included diarrhea (72%), hypophosphatemia (61%), nausea (61%), vomiting (44%), fatigue (44%), decreased appetite (36%), rash (31%), hypokalemia (28%) and pruritus (25%). In addition, TRSAEs experienced by more than one subject included diarrhea (8%) and nausea (8%).

AL101 for the Treatment of R/M Adenoid Cystic Carcinoma

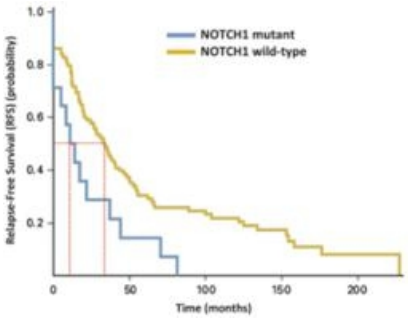
Disease Background

ACC is a rare solid tumor malignancy of secretory glands including the salivary glands. While major salivary glands are located in the mouth, minor salivary glands are scattered throughout the aerodigestive tract and are mostly concentrated in cheeks, lips, tongue, palate and floor of the mouth. ACC can also arise in other sites outside the head and neck. When presenting in the major salivary glands, ACC can cause symptoms of varying severity, including numbness, difficulty swallowing or paralysis of a facial nerve.

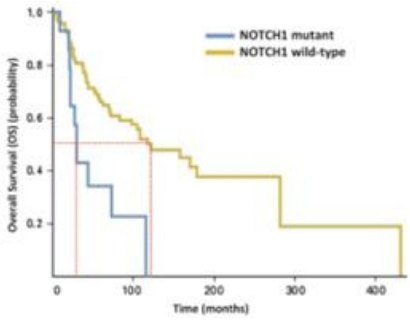
ACC is characterized by its high recurrence rate and, along with its persistent and relentless progressive course, often manifests as local recurrences and late-onset distant metastasis. ACC has an annual incidence of approximately 3,400 patients in the United States, approximately 1,700 of which are R/M ACC patients. Based on primary literature and our bioinformatics research, we estimate that 18% to 22% of R/M ACC patients have Notch-activating mutations.

Notch Is a Tumorigenic Driver in ACC and
Correlates with a Distinct Pattern of Metastases and Poor Prognosis

Median RFS = 12.5 vs 33.9 months (*p=0.01*)



Median OS = 29.6 vs 121.9 months (*p=0.001*)



Data from MD Anderson Cancer Center

As the understanding of the biology of cancer and ACC specifically evolved, the importance of the Notch pathway and Notch-activating mutations was established. A recent publication from MD Anderson Cancer Center examined the relationship between Notch-activating mutations and ACC patient prognosis in 102 subjects, as illustrated in the figures above. The figure on the left shows that the relapse free survival, or time from diagnosis to relapse, was reduced from 33.9 months for Notch 1 wild-type, or WT, patients to 12.5 months for Notch 1 mutant patients. In addition, patients with Notch-activating mutations were more likely to present with advanced-stage disease and they developed a somewhat different pattern of metastatic disease compared to Notch 1 WT patients. Similarly, the graphic on the right demonstrates that median overall survival was reduced from 121.9 months for Notch 1 WT patients to 29.6 months for Notch 1 mutant patients. Similar results were subsequently observed in an additional retrospective study analyzing data from 84 ACC subjects at Memorial Sloan Kettering Cancer Center, where median overall survival was reduced from 204.5 months for Notch 1 WT patients to 55.1 months for Notch 1 mutant patients.

Current Treatment Landscape

The current standard of care is typically surgery followed by radiation. Radiation or systemic therapy, comprised of chemotherapy and targeted drugs, may be recommended if the tumor cannot be surgically removed or in cases of advanced metastatic disease. There are limited systemic therapy treatment options, and no FDA-approved therapies, available for patients with R/M ACC. According to the Surveillance, Epidemiology, and End Results, or SEER, the relative survival rate for all ACC patients in the United States between 1975 and 2016 was 81% at five years and 66% at ten years. Treatment has been particularly ineffective for ACC patients with metastatic disease, where survival rates are much lower: 33% at five years and 24% at ten years. According to published data from 31 Phase 2 clinical trials in ACC conducted since 2005 using a variety of treatment modalities, these treatments showed limited or no clinical activity in unselected ACC subjects. The ORR in 30 of these trials ranged from 0% to 20%, with a 47% ORR observed in one trial conducted in China. In 15 of the 31 trials, a 0% ORR was observed. Accordingly, there remains a lack of effective treatment options for patients with R/M ACC.

Our Proposed Solution for R/M ACC: AL101

We are developing AL101 as a potent, selective and injectable small molecule GSI for patients with R/M ACC with Notch-activating mutations and we believe that AL101 has the potential to be the first FDA-approved therapy for this patient population.

Our Ongoing Phase 2 ACCURACY Trial:

We are currently evaluating subjects in our ongoing Phase 2 ACCURACY trial of AL101 as a monotherapy for the treatment of R/M ACC. Our Phase 2 ACCURACY trial is an open-label, single-arm, multi-center study of AL101 administered intravenously, or IV, in subjects with ACC bearing Notch-activating mutations who have previously been treated for or are newly diagnosed with metastatic disease.

The primary endpoint of our Phase 2 ACCURACY trial is the objective response rate as measured by Response Evaluation Criteria in Solid Tumors, or RECIST, 1.1, a commonly used set of measures for evaluating the response of solid tumors to treatment, with confirmation by an independent review committee. Secondary endpoints include objective response rate by investigator review, duration of response and progression-free survival by an independent review committee and an investigator review, overall survival, safety and tolerability and pharmacokinetics, or PK. The Phase 2 ACCURACY trial is powered to assess statistical significance for these endpoints. However, the Phase 2 ACCURACY trial is ongoing and formal statistical testing will not be performed until the study is complete.

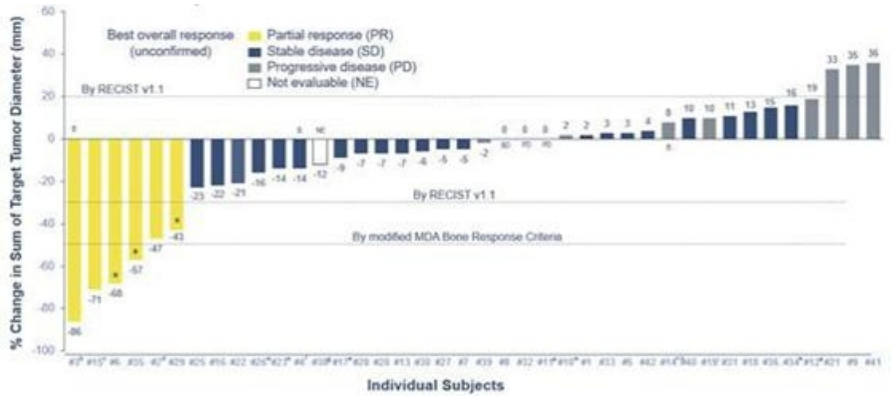
Part 1 of the trial dosed 45 subjects at 4 mg of AL101 IV once weekly. Stage 2 of the trial dosed additional 42 subjects at 6 mg of AL101 IV once weekly.

Ongoing Phase 2 ACCURACY Trial Interim Clinical Data – 4mg:

Our interim data from the 4 mg dosing group of our Phase 2 ACCURACY trial as of July 30, 2020 showed early signs of clinical activity. As of July 30, 2020, 40 subjects were evaluable for a response using RECIST 1.1. No CRs were observed, three confirmed and three unconfirmed PRs (which will remain unconfirmed) were observed in six subjects, and SD was observed in 21 subjects, yielding a 68% disease control rate among the evaluable subjects. All six subjects with either confirmed or unconfirmed PRs had received prior radiation therapy and four subjects had received prior systemic chemotherapy.

The best objective responses observed in the 4mg cohort of our Phase 2 ACCURACY trial, as determined by the investigator and measured by RECIST 1.1, are shown in the following graph, by individual subject. The dotted lines under the x-axis represent cutoffs for PR, defined as a 30% or greater reduction in the sum of the longest diameters of target lesions for RECIST 1.1 or, for bone-only disease patients, a 50% or greater reduction in lesion size for the MD Anderson modified bone response criteria. Progressive disease is defined as a 20% or greater increase in the sum of the longest diameters. Stable disease is reflected between the dotted lines at 20% and -30%.

Best Objective Responses by Investigator Review (n=40)a



Data as of data collection cutoff date of July 30, 2020.

B = bone-only disease.

NE = Not Evaluable for Response.

* Confirmed responses.

a) Includes efficacy-evaluable subjects only. #24 not included because the patient withdrew consent; #37 not included because died before disease assessment.

b) Subject #3, with bone-only disease, had an unconfirmed PR at week 32 by the investigator per modified MDA Bone Response Criteria.

c) Subject #15 had an unconfirmed PR at week 8.

d) Subject #2 had an unconfirmed PR at week 16.

e) These subjects had clinical PD.

f) Subject #4, with bone-only disease, had SD at week 16 by the investigator per modified MDA Bone Response Criteria.

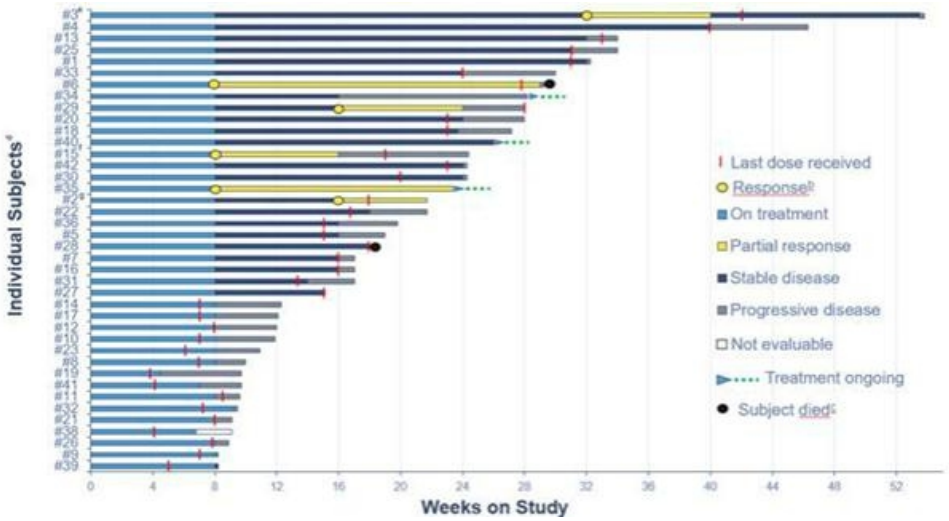
g) Subject #38 was NE because only one scan demonstrating SD was performed at week 7.

h) Subject #14, with bone-only disease, had PD at week 8 by the investigator per modified MDA Bone Response Criteria.

i) Subject #19 had radiographic PD.

The following graph depicts the treatment duration and clinical response of subjects in our 4mg cohort of our Phase 2 ACCURACY trial as of July 30, 2020. Time to PR is denoted using yellow circles and the three subjects who remain on therapy as of the data cutoff are denoted using blue arrows. Radiographic evaluations are performed every eight weeks and the first point at which a subject achieved a PR is indicated by the change in line color following the yellow response circles.

Time of Objective Response by Investigator Review (n=40)a



Data as of data collection cutoff date of July 30, 2020.

a) Represents all efficacy-evaluable subjects.

b) Response as assessed by investigator per RECIST v1.1.

c) Only deaths occurring within 30 days after the last dose are shown.

d) Subject #3, Subject #4 and Subject #14 had bone-only disease.

e) Subject #3 had an unconfirmed PR at week 32 by the investigator per modified MDA Bone Response Criteria.

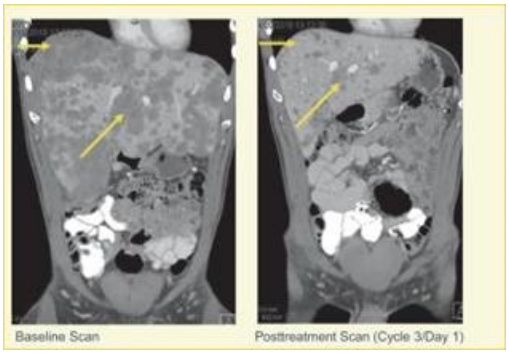
f) Subject #15 had an unconfirmed PR at week 8.

g) Subject #2 had an unconfirmed PR at week 16.

The figures below are radiographic scan results from four subjects participating in our 4mg cohort of our Phase 2 ACCURACY trial who exhibited either a confirmed PR (subjects #6, #29 and #35) or unconfirmed PR (subject #15).

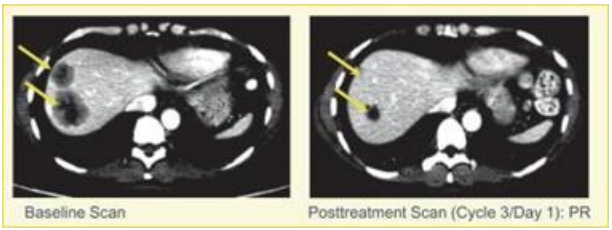
- Subject #6 was a 29 year-old male with extensive metastatic liver disease and significant right upper quadrant pain related to the enlargement of his liver. He had received prior therapy with radiation and chemotherapy treatments but the disease progressed despite these therapies. This subject exhibited gradual improvements during the clinical trial and a confirmed PR was observed at week 8. Subject #6 died shortly after week 28, within 30 days of AL101 treatment.

Subject #6



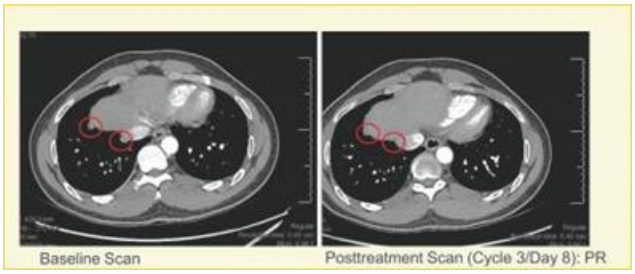
- Subject #15 was a 47 year-old female with metastatic liver disease. She had received prior therapy with surgery, radiation and chemotherapy treatments but the disease progressed despite these therapies. On trial, a substantial shrinkage of disease in this subject's liver was observed and a PR was observed at week 8. Subject #15 ended treatment after progressive disease was observed at week 16.

Subject #15



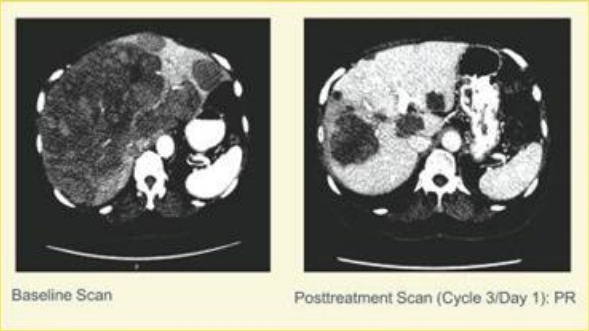
- Subject #29 is a 36 year-old male with metastatic lung disease. He had received prior therapy with surgery and radiation, but the disease progressed despite these therapies. On trial, a confirmed PR was observed in this subject's lung at week 8. Subject #29 ended treatment after disease progression was observed at week 24.

Subject #29



- Subject #35 is a 76 year-old female with metastatic liver disease. She had received prior therapy, including systemic chemotherapy, but the disease progressed. On trial, a confirmed PR was observed in this subject's liver at week 8. As of July 30, 2020, Subject #35 remained on trial.

Subject #35



We have observed subjects who showed response following their first radiographic exam at eight weeks after treatment. We believe that these interim results provide evidence supporting continue development of AL101 as a monotherapy for patients with R/M ACC. We expect to release additional interim results from our Phase 2 ACCURACY trial at a medical conference in the second half of 2022.

Phase 2 ACCURACY Trial Interim Safety Results for the 4mg Cohort

AL101 at 4mg Q1w regimen was generally observed to be well tolerated in the interim data as of July 30, 2020, with most adverse events being mild to moderate in severity. All subjects experienced at least one treatment-related adverse event, or TRAE, while approximately 20% experienced a Grade 3 or 4 TRAE. In addition, seven subjects experienced a total of eight treatment-related serious adverse events, or TRSAEs. The eight TRSAEs included two Grade 2 infusion reactions, one Grade 1 keratoacanthoma, one Grade 3 aspartate aminnotransferase increase, one Grade 3 pneumonia, one Grade 3 decreased appetite, one Grade 3 transient ischemic attack (TIA) and one Grade 4 hyponatremia. Eight subjects had a dose reduction from 4 mg to 2.4 mg, six of which were within two weeks of an adverse event. There were 17 dose interruptions resulting in delays of at least one week due to adverse events, most of which were no more than two weeks in length. Five subjects began treatment but discontinued before their first post-dose radiographic evaluation. Of these five subjects, one subject discontinued due to an infusion reaction, one due to pneumonia, two subjects discontinued due to non-treatment related adverse events and one subject stopped treatment without a first follow-up radiographic evaluation. Therefore, these five subjects were considered non-evaluable for efficacy. There were four deaths within 30 days of stopping AL101 treatment, which were assessed by the investigator not to be treatment-related. One additional death was reported for a subject who was not evaluated for efficacy. This death was assessed by the investigator to likely be treatment-related, though assessed by the trial sponsor to likely be the result of advanced disease and/or pneumonia. The following chart depicts the TRAEs observed in our Phase 2 ACCURACY trial, as of the data cutoff date of June 30, 2020.

TRAEs Reported in [3]15% of Subjects in the 4mg Cohort

	Safety Population (N=45)[b] 4 mg IV QW	
	Any Grade, n (%)	Grade 3/4, n (%)
Any TRAE	**45 (100)**	**9 (20)**
Diarrhea	27 (60)	2 (4)
Fatigue	23 (51)	2 (4)
Nausea	22 (49)	1 (2)
Hypophosphatemia	19 (42)	2 (4)
Cough	12 (27)	0
Vomiting	12 (27)	0
Epistaxis	9 (20)	0
Rash maculo-papular	8 (18)	0
Decreased appetite	7 (16)	1 (2)
Dysgeusia	7 (16)	0

Data as of data collection cutoff date of July 30, 2020.

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living, or instrumental ADL, which refers to activities such as preparing meals, shopping for groceries or clothes, using the telephone and managing money.

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL, which refers to bathing, dressing and undressing, feeding one's self, using the toilet, taking medications, and not being bedridden.

Grade 4: Life-threatening consequences; urgent intervention indicated.

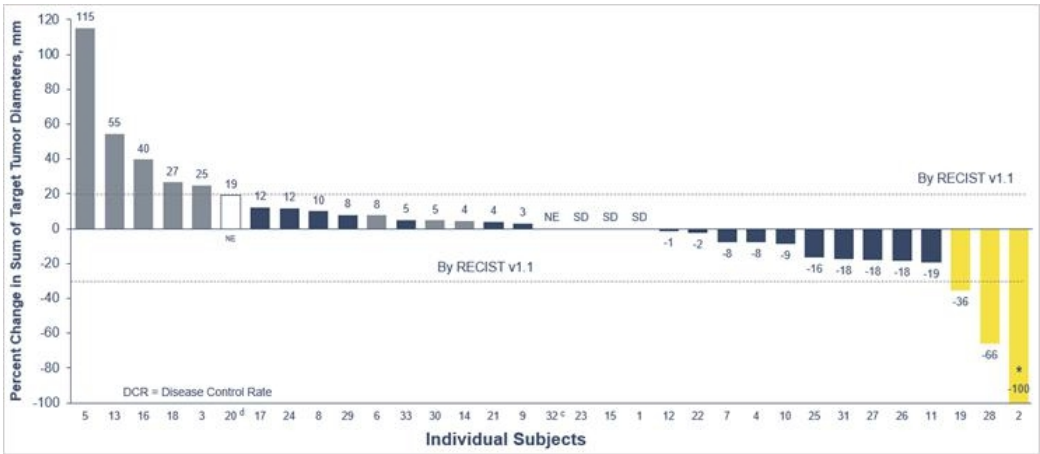
* 8 events were Grade 3, one was Grade 4

Ongoing Phase 2 ACCURACY Trial Interim Clinical Data – 6mg:

Our interim data from the 6mg dosing group of our Phase 2 ACCURACY trial as of July 9, 2021 include 33 subjects that were evaluable for a response using RECIST 1.1. No CRs were observed, two confirmed and one unconfirmed PRs (which will remain unconfirmed) were observed in three subjects, and SD was observed in 20 subjects, yielding a 60.6% disease control rate among the evaluable subjects.

The best objective responses observed in our 6mg cohort of the Phase 2 ACCURACY trial, as determined by the investigator and measured by RECIST 1.1, are shown in the following graph, by individual subject. The dotted lines under the x-axis represent cutoffs for PR, defined as a 30% or greater reduction in the sum of the longest diameters of target lesions for RECIST 1.1 or, for bone-only disease patients, a 50% or greater reduction in lesion size for the MD Anderson modified bone response criteria. Progressive disease is defined as a 20% or greater increase in the sum of the longest diameters. Stable disease is reflected between the dotted lines at 20% and -30%.

Best Objective Responses by Investigator Review (n=33)[a,b]



Data cutoff as of July 9, 2021.

a. Response as assessed by investigator per RECIST version 1.1.

b. Includes all efficacy-evaluable patients.

c. Patient #32 had a best overall response of NE because no post baseline measurements were recorded but is included here as zero for completeness.

d. Patient #20 had a best overall response of NE; the percent change calculation excludes tumors that are measured at screening only (T5).

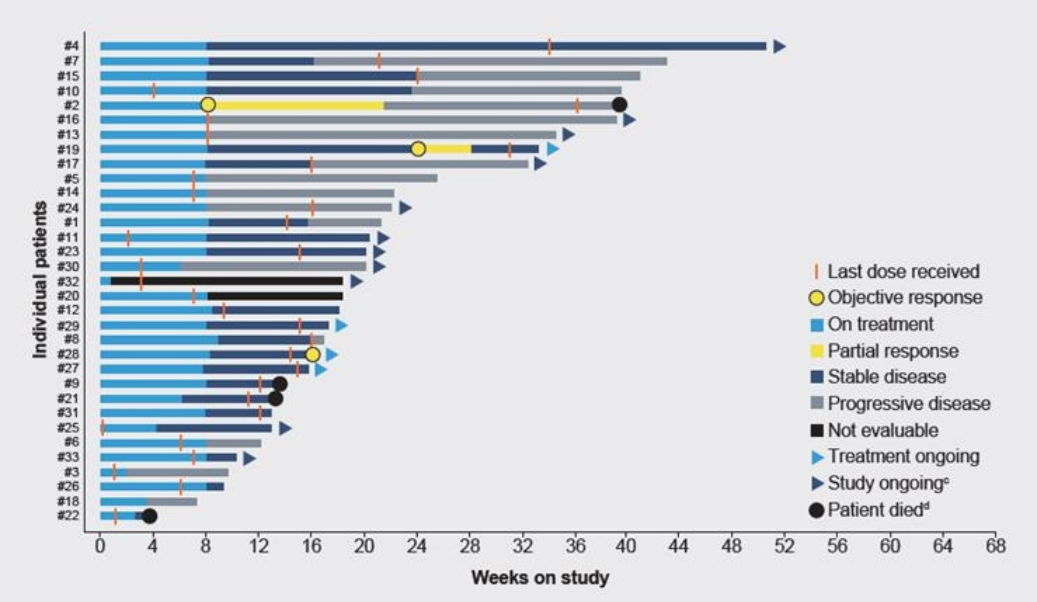
* = Confirmed responses.

** = Unconfirmed response.

DCR = disease control rate
NE = not evaluable
PD = progressive disease
PR = partial response
RECIST = Response Evaluation Criteria in Solid Tumors
SD = stable disease.

The following graph depicts the treatment duration and clinical response of subjects in our 6mg cohort of the Phase 2 ACCURACY trial as of July 09, 2021. Time to PR is denoted using yellow circles and the three subjects who remain on therapy as of the data cutoff are denoted using blue arrows. Radiographic evaluations are performed every eight weeks and the first point at which a subject achieved a PR is indicated by the change in line color following the yellow response circles.

Time of Objective Response [a] by Investigator Review (n=33)[b]



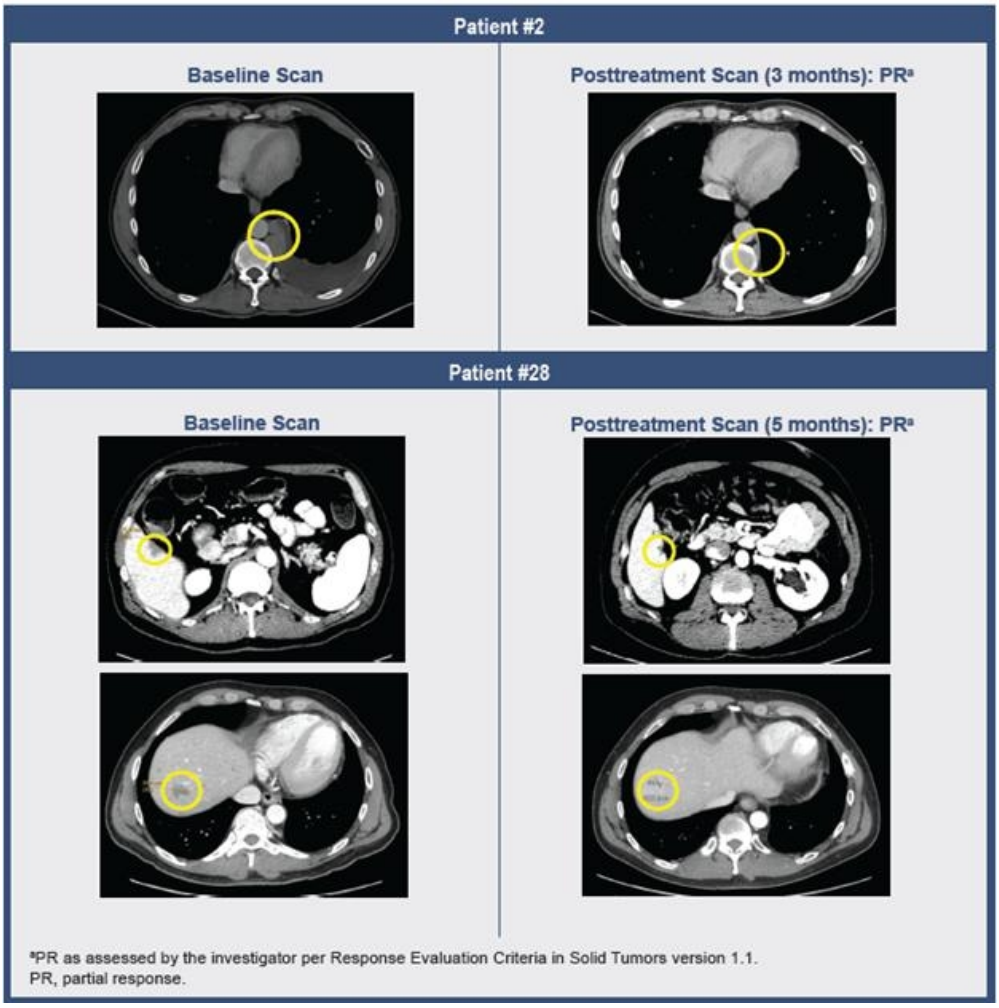
a. Response as assessed by the investigator per Response Evaluation Criteria in Solid Tumors version 1.1.

b. Includes all efficacy-evaluable patients (of note, patients #20 and #32 are not evaluable).

c. These patients have stopped treatment but they are still being followed.

d. Within 30 days of treatment end date.

The figures below are radiographic scan results from two subjects participating in the 6mg cohort of our Phase 2 ACCURACY trial who exhibited Partial Responses with AL101 6-mg treatment.



Phase 2 ACCURACY Trial 6mg cohort Interim Safety Results

All 42 treated patients in the AL101 6-mg cohort experienced treatment-emergent AEs, or TEAEs, which were treatment related in 41 patients (97.6%; See table below). Thirty-two patients (76.2%) in the AL101 6-mg cohort had grade 3/4 AEs, which were treatment related in 27 patients (64.3%; See table below). Twenty-six patients (61.9%) reported at least 1 serious TEAEs in the AL101 6-mg cohort, 13 (31.0%) of which were considered to be treatment related (See table below). There were 4 deaths (9.5%) resulting from TEAEs in the AL101 6-mg cohort (See table below).

6mg cohort Safety Summary table:

	AL101 6-mg (N=42)	
	Treatment emergent, n (%)	Treatment related, n (%)
Any AE	42 (100)	41 (97.6)
Any grade 3/4 AE	32 (76.2)	27 (64.3)
Any SAE	26 (61.9)	13 (31.0)
Any deaths	4 (9.5)	1 (2.4)*
AEs leading to discontinuation of AL101	11 (26.2)	NA
AEs requiring dose interruption of AL101	25 (59.5)	NA
AEs requiring dose reduction of AL101	10 (23.8)	NA
AEs requiring dose delays of AL101	2 (2.0)	NA

Data cutoff as of July 9, 2021.
*Acute respiratory distress syndrome.
AE, adverse event; NA, not available; SAE serious adverse event.

Treatment-related diarrhea was common and occurred in 32 (76.2%) patients in the AL101 6-mg cohort (Table 3), consistent with reports of NOTCH pathway inhibition. Most events were grade 1/2 in 26 (61.9%) patients in the AL101 6-mg cohort. Treatment-related serious diarrhea occurred in 4 patients (9.5%) in the AL101 6mg cohort.

Treatment-Related AEs Reported in ≥15% of Patients

	AL101 6-mg (N=42)	
	Any grade, n (%)	Grade 3/4, n (%)
Diarrhea	32 (76.2)	6 (14.3)
Fatigue	20 (47.6)	2 (4.8)
Nausea	17 (40.5)	2 (4.8)
Hypophosphatemia	12 (28.6)	1 (2.4)
Vomiting	11 (26.2)	2 (4.8)
Decreased appetite	11 (26.2)	1 (2.4)
Dry mouth	9 (21.4)	0
Rash	9 (21.4)	0
Cough	8 (19.0)	0
Dermatitis acneiform	7 (16.7)	0
Epistaxis	7 (16.7)	0
Rash maculo-papular	6 (14.3)	2 (4.8)

Data cutoff as of July 9, 2021.
AE, adverse event.

Regulatory Approval Strategy

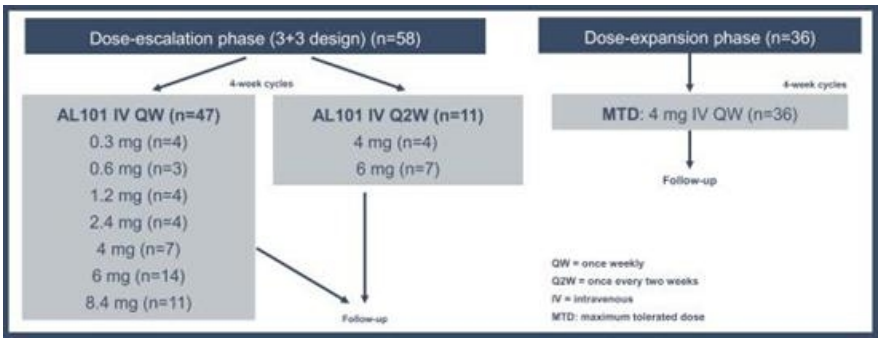
The FDA has granted Orphan Drug Designation to AL101 for the treatment of ACC. In addition, the FDA has granted fast track designation to AL101 for the treatment of R/M ACC. Given the significant unmet medical need and lack of FDA-approved therapies for patients with R/M ACC, we may seek a potential expedited regulatory review pathway pending additional results from the ongoing Phase 2 ACCURACY trial.

Phase 1 Studies

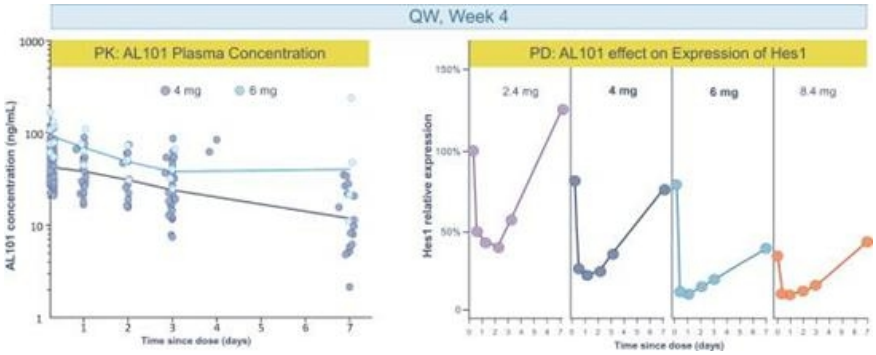
BMS evaluated AL101 in more than 200 unselected subjects with various cancers across three Phase 1 studies. While these Phase 1 studies did not report statistically significant overall results, clinical activity was observed in cancers in which activation of the Notch pathway is a known tumorigenic driver. In these Phase 1 studies, the recommended clinical dose for our ongoing Phase 2 ACCURACY trial was established. A summary of the three Phase 1 studies is below.

CA216001

In a Phase 1 study of AL101 in heavily pretreated subjects with advanced or metastatic tumors, which we refer to as the CA216001 study, AL101 IV was administered as a monotherapy. A total of 58 subjects were evaluated in the dose-escalation phase and an additional 36 subjects were evaluated in the dose-expansion phase. Of these subjects, 43 were treated with 4 mg of AL101 IV once weekly and 14 subjects were treated with 6 mg of AL101 IV once weekly. An additional 11 subjects were treated in a twice-weekly dosing arm and received either 4 mg or 6 mg of AL101 IV twice weekly. The primary objective of the CA216001 study was to evaluate the safety and tolerability of AL101. Secondary objectives included evaluating the PK, pharmacodynamics, or PD, changes in the expression of Notch-induced genes and the anti-tumor activity of AL101. Formal statistical testing for these endpoints was not performed and the results were presented as descriptive statistics. The design of this study, including dose groupings, is depicted below.



Of the 94 subjects evaluated in this study, two subjects had ACC and three subjects had desmoid tumors. PRs were observed in three subjects, including one subject with ACC and two subjects with desmoid tumors. In addition, SD was observed in 10 subjects, including one subject with ACC and one subject with desmoid tumors. As shown in the below graphs, the PK of AL101 was linear, with dose-dependent increases in exposure that correlated with suppression of the PD marker Hes1.



Subjects enrolled in the CA216001 study were heavily pretreated, with over 70% of subjects previously undergoing at least three lines of prior therapy. AL101 was generally observed to be well tolerated at the dose chosen for our Phase 2 ACCURACY trial. During the course of the study, there were 27 deaths, including one death due to hepatic failure in the highest weekly dose tested (8.4 mg) that was assessed by the investigator to be treatment-related. Treatment was discontinued in nine subjects due to TRAEs. Approximately 89% of subjects experienced at least one TRAE and approximately 51% of subjects experienced at least one Grade 3 or 4 TRAEs. In addition, approximately 16% of subjects dosed with 4 mg and approximately 29% of subjects dosed with 6 mg experienced TRSAEs. The following table represents the most commonly reported TRAEs.

TRAEs reported in ≥15% of all treated subjects	Subjects treated with AL101 4 mg QW (n=43)		Subjects treated with AL101 6 mg QW (n=14)		All AL101 treated subjects (n=94)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Diarrhea, n (%)	29 (67)	8 (19)	10 (71)	6 (43)	59 (63)	18 (19)
Hypophosphatemia, n (%)	26 (60)	18 (42)	11 (79)	7 (50)	50 (53)	33 (35)
Fatigue, n (%)	15 (35)	0	11 (79)	0	42 (45)	1 (1)
Nausea, n (%)	18 (42)	1 (2)	10 (71)	0	41 (44)	1 (1)
Vomiting, n (%)	13 (30)	1 (2)	5 (36)	1 (7)	28 (30)	4 (4)
Decreased appetite, n (%)	11 (26)	0	6 (43)	0	25 (27)	0
Hypokalemia, n (%)	9 (21)	3 (7)	3 (21)	1 (7)	15 (16)	6 (6)

QW = once weekly

The results from this Phase 1 study of AL101 supported advancing the once weekly dosing regimen of 4 mg or 6 mg and showed early signs of clinical activity across solid tumor types. In addition, AL101 was generally observed to be well tolerated at the dose chosen for our Phase 2 ACCURACY trial.

CA216002

In a Phase 1 study of AL101 in 31 heavily pretreated subjects, which included four T-LL subjects and 27 T-ALL subjects, AL101 IV was administered QW, or once weekly, as a monotherapy. We refer to this study as the CA216002 study. A total of 17 subjects were evaluated in the dose-escalation phase and an additional 14 subjects were evaluated in the dose-expansion phase. The primary objective of the CA216002 study was to evaluate the safety and tolerability of AL101. Secondary objectives included evaluating the PK, PD changes in the expression of Notch-induced genes and the anti-tumor activity of AL101. Formal statistical testing for these endpoints was not performed and the results were presented as descriptive statistics. The design of this study, including dose groupings, is depicted below.

Dose-escalation Phase (3+3 design) (n=17) **Dose-expansion Phase (n=14)**

A total of 26 T-ALL subjects in this study received either a 4 mg or 6 mg dosage of AL101, 11 of whom had Notch 1 mutations. Objective responses were observed in three subjects with T-ALL, each in the 6 mg dose group, with CRs observed in two subjects and a PR observed in one subject. Of these three subjects, two had Notch 1 mutations. Following the administration of AL101, eight subjects with T-ALL experienced a 50% or greater reduction in leukemic blasts in bone marrow.

Subjects enrolled in the CA216002 study were heavily pretreated, with over 50% of subjects previously undergoing at least three lines of prior therapy. AL101 was generally well tolerated during the study. During the course of the study, there were 20 deaths, including one patient in the 4 mg once weekly dosing group who was heavily pretreated with at least four prior systemic therapies and died due to gastrointestinal hemorrhage. While this patient's death was assessed by the investigator not to be treatment-related, BMS determined that it was possible the death was treatment-related. Treatment was discontinued in one subject due to TRAEs. Approximately 74% of subjects experienced at least one TRAE and approximately 23% of subjects experienced at least one Grade 3 or 4 TRAEs. In addition, approximately 16% of subjects experienced TRSAEs, which included single events of hepatoxicity and hypersensitivity in the 4 mg dose cohort and single events of anemia, diarrhea and infusion-related reaction in the 6 mg dose cohort. The following table represents the most commonly reported TRAEs.

TRAEs reported in ≥ 15% of all treated subjects	Subjects treated with AL101 4 mg QW (n=10)		Subjects treated with AL101 6 mg QW (n=20)		All AL101 treated subjects (n=31)	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Diarrhea, n (%)	3 (30)	1 (10)	12 (60)	0	15 (48)	1 (3)
Nausea, n (%)	1 (10)	0	4 (20)	0	5 (16)	0
Vomiting, n (%)	0	0	4 (20)	0	4 (13)	0

The results from this Phase 1 study of AL101 supported advancing the anticipated once weekly dosing regimen of 6 mg, as this dose showed signs of clinical activity and was generally observed to be well tolerated.

CA216003

In a Phase 1 study in heavily pretreated subjects with advanced or metastatic solid tumors, which we refer to as the CA216003 study, AL101 IV was administered in combination with three different chemotherapy regimens. A total of 95 subjects were evaluated in the study, with 90 subjects receiving both chemotherapy and AL101. The primary objective of the CA216003 study was to evaluate the safety and tolerability of AL101 in combination with chemotherapy. Secondary objectives included evaluating the PK of AL101 in combination with chemotherapy, PD changes in the expression of Notch-induced genes after treatment with AL101 in combination with chemotherapy and the anti-tumor activity of AL101 in combination with chemotherapy. Formal statistical testing for these endpoints was not performed and the results were presented as descriptive statistics.

Of the 95 subjects evaluated in this study, 22 subjects had TNBC. Of the TNBC subjects, a CR was observed in one subject, PRs were observed in seven subjects and SD was observed in five subjects.

Subjects enrolled in the CA216003 study were heavily pretreated, with 40% of subjects previously undergoing at least three lines of prior therapy. AL101 in combination with chemotherapy was generally observed to be well tolerated during the study. During the course of the study, there were 32 deaths, but none were assessed by the investigator or BMS to be treatment-related. Treatment was discontinued in 15 subjects due to TRAEs. Nearly all subjects experienced at least one TRAE and approximately 82% of subjects experienced at least one Grade 3 or 4 TRAE. In addition, approximately 34% of subjects experienced TRSAEs. The most commonly reported Grade 3 or 4 TRSAEs included febrile neutropenia (10%) and diarrhea (6%). The most commonly reported TRAEs included: fatigue (78%), diarrhea (63%), hypophosphatemia (62%), nausea (52%), decreased appetite (46%), vomiting (39%), alopecia (38%), anemia (31%), neutropenia (26%), rash (26%), dysgeusia, or distortion of the sense of taste, (20%), dehydration (19%), weight decrease (18%), thrombocytopenia, or low blood platelet count, (17%), hypokalemia, or low potassium levels, (17%), stomatitis, or inflammation of the mouth and lips, (16%) and myalgia, or muscle soreness (16%).

License Agreements

Bristol-Myers Squibb Company License Agreement

In November 2017, we entered into a license agreement, or the BMS License Agreement, with BMS, under which BMS granted us a worldwide, non-transferable, exclusive, sublicensable license under certain patent rights and know-how controlled by BMS to research, discover, develop, make, have made, use, sell, offer to sell, export, import and commercialize AL101 and AL102, or the BMS Licensed Compounds, and products containing AL101 or AL102, or the BMS Licensed Products, for all uses including the prevention, treatment or control of any human or animal disease, disorder or condition.

Under the BMS License Agreement, we are obligated to use commercially reasonable efforts, either through ourselves or through our affiliates or sublicensees, to develop at least one BMS Licensed Product. As between BMS and us, we have sole responsibility for, and bear the cost of, conducting research and development and preparing all regulatory filings and related submissions with respect to the BMS Licensed Compounds and/or BMS Licensed Products. BMS has assigned and transferred all INDs for the BMS Licensed Compounds to us. We are also required to use commercially reasonable efforts to obtain regulatory approvals in certain major market countries for at least one BMS Licensed Product, as well as to commercialize and sell each BMS Licensed Product after obtaining such regulatory approval. As between BMS and us, we have sole responsibility for, and bear the cost of, commercializing BMS Licensed Products. For a limited period of time, we may not, either by ourselves or through our affiliates, sublicensees, or any other third parties, engage directly or indirectly in the clinical development or commercialization of a Notch inhibitor molecule that is not a BMS Licensed Compound.

As consideration of the rights granted by BMS to us under the BMS License Agreement, we paid BMS a payment of $6 million and issued to BMS 1,125,929 shares of Series A preferred stock valued at approximately $7.3 million. We are required to pay BMS payments upon the achievement of certain development or regulatory milestone events of up to $95 million in the aggregate with respect to the first BMS Licensed Compound to achieve each such event and up to $47 million in the aggregate with respect to each additional BMS Licensed Compound to achieve each such event. We are also obligated to pay BMS payments of up to $50 million in the aggregate for each BMS Licensed Product that achieves certain sales-based milestone events and tiered royalties on net sales of each BMS Licensed Product by us or our affiliates or sublicensees at rates ranging from a high single-digit to low teen percentage, depending on the total annual worldwide net sales of each such Licensed Product. If we sublicense or assign any rights to the licensed patents, the BMS Licensed Compounds and/or the BMS Licensed Products, we are required to share with BMS a portion of all consideration we receive from such sublicense or assignment, ranging from a mid-teen to mid-double-digit percentage, depending on the development stage of the most advanced BMS Licensed Compound or BMS Licensed Product that is subject to the applicable sublicense or assignment, but such portion may be reduced based on the milestone or royalty payments that are payable by us to BMS under the BMS License Agreement.

The BMS License Agreement remains in effect, on a country-by-country and BMS Licensed Product-by-BMS Licensed Product basis, until the expiration of royalty obligations with respect to a given BMS Licensed Product in the applicable country. Royalties are paid on a country-by-country and BMS Licensed Product-by-BMS Licensed Product basis from the first commercial sale of a particular BMS Licensed Product in a country until the latest of (a) 10 years after the first commercial sale of such BMS Licensed Product in such country, (b) when such BMS Licensed Product is no longer covered by a valid claim in the licensed patent rights in such country, or (c) the expiration of any regulatory or marketing exclusivity for such BMS Licensed Product in such country.

Any inventions, and related patent rights, invented solely by either party pursuant to activities conducted under the BMS License Agreement shall be solely owned by such party, and any inventions, and related patent rights, conceived of jointly by us and BMS pursuant to activities conducted under the BMS License Agreement shall be jointly owned by us and BMS, with BMS's rights thereto included in our exclusive license. We have the first right—with reasonable consultation with, or participation by, BMS—to prepare, prosecute, maintain and enforce the licensed patents, at our expense.

BMS has the right to terminate the BMS License Agreement in its entirety upon written notice to us (a) for insolvency-related events involving us, (b) for our material breach of the BMS License Agreement if such breach remains uncured for a defined period of time, (c) for our failure to fulfill our obligations to develop or commercialize the BMS Licensed Compounds and/or BMS Licensed Products not remedied within a defined period of time following written notice by BMS, or (d) if we or our affiliates commence any action challenging the validity, scope, enforceability or patentability of any of the licensed patent rights. We have the right to terminate the BMS License Agreement (a) for convenience upon prior written notice to BMS, the length of notice dependent on whether a BMS Licensed Product has received regulatory approval, (b) upon immediate written notice to BMS for insolvency-related events involving BMS, (c) for BMS's material breach of the BMS License Agreement if such breach remains uncured for a defined period of time, or (d) on a BMS Licensed Compound-by-BMS Licensed Compound and/or BMS Licensed Product-by-BMS Licensed Product basis upon immediate written notice to BMS if we reasonably determine that there are unexpected safety and public health issues relating to the applicable BMS Licensed Compounds and/or BMS Licensed Products. Upon termination of the BMS License Agreement in its entirety by us for convenience or by BMS, we grant an exclusive, non-transferable, sublicensable, worldwide license to BMS under certain of our patent rights that are necessary to develop, manufacture or commercialize BMS Licensed Compounds or BMS Licensed Products. In exchange for such license, BMS must pay us a low single-digit percentage royalty on net sales of the BMS Licensed Compounds and/or BMS Licensed Products by it or its affiliates, licensees or sublicensees, provided that the termination occurred after a specified developmental milestone for such BMS Licensed Compounds and/or BMS Licensed Products.

Novartis International Pharmaceutical Limited Evaluation, Option and License Agreement

In December 2018, we entered into an evaluation, option and license agreement, or the Novartis Agreement, with Novartis International Pharmaceutical Limited, or Novartis, pursuant to which Novartis agreed to conduct certain studies to evaluate AL102 in combination with its B-cell maturation antigen, or BCMA, therapies in multiple myeloma, and we agreed to supply AL102 for such studies. All supply and development costs associated with such evaluation studies are fully borne by Novartis.

Under the Novartis Agreement, we granted Novartis an exclusive option to obtain an exclusive (including as to us and our affiliates), sublicensable (subject to certain terms and conditions), worldwide license and sublicense (as applicable) under certain patent rights and know-how controlled by us (including applicable patent rights and know-how that are licensed from BMS pursuant to the BMS License Agreement) to research, develop, manufacture (subject to our non-exclusive right to manufacture and supply AL102 and/or the Novartis Licensed Product for Novartis) and commercialize AL102 and/or any pharmaceutical product containing AL102 as the sole active ingredient, or the Novartis Licensed Product, for the diagnosis, prophylaxis, treatment, or prevention of multiple myeloma in humans. We also granted Novartis the right of first negotiation for the license rights to conduct development or commercialization activities with respect to the use of AL102 for indications other than multiple myeloma. Additionally, from the exercise by Novartis of its option until the termination of the Novartis Agreement, we may not, either ourselves or through our affiliates or any other third parties, directly or indirectly research, develop or commercialize certain BCMA-related compounds for the treatment of multiple myeloma.

Novartis must pay us a low eight figure option exercise fee in order to exercise its option and activate its license, upon which we will be eligible to receive development, regulatory and commercial milestone payments of up to $245 million in the aggregate and tiered royalties on net sales of Novartis Licensed Products by Novartis or its affiliates or sublicensees at rates ranging from a mid-single-digit to low double-digit percentage, depending on the total annual worldwide net sales of Novartis Licensed Products. Royalties will be paid on a country-by-country and Novartis Licensed Product-by-Novartis Licensed Product basis from the first commercial sale of a particular Novartis Licensed Product in a country until the latest of (a) 10 years after the first commercial sale of such Novartis Licensed Product in such country, (b) when such Novartis Licensed Product is no longer covered by a valid claim in the licensed patent rights in such country, or (c) the expiration of any regulatory or marketing exclusivity for such Novartis Licensed Product in such country. Contemporaneously with the Novartis Agreement, we entered into a stock purchase agreement and associated investment agreements, or the SPA, with Novartis's affiliate, Novartis Institutes for BioMedical Research, Inc., or NIBRI, pursuant to which NIBRI acquired a $10 million equity stake in us.

Novartis shall own any inventions, and related patent rights, invented solely by it or jointly with us in connection with activities conducted pursuant to the Novartis Agreement. We will maintain first right to prosecute and maintain any patents licensed to Novartis, both before and after its exercise of its option. We maintain the first right to defend and enforce our patents prior to Novartis's exercise of its option, upon which Novartis gains such right with respect to patents included in the license.

The option we granted to Novartis will remain in effect until the earlier of (a) 60 days following the last visit of the last subject in the evaluation studies, (b) the termination of the Novartis Agreement, or (c) 36 months following the delivery by us to Novartis of sufficient amounts of clinical evaluation materials to conduct the anticipated clinical studies. The Novartis Agreement remains in effect until such time as no Novartis Licensed Product is being developed or commercialized by Novartis, its affiliates, or sublicensees (including distributors or commercial partners), unless terminated earlier. We have the right to terminate the Novartis Agreement (a) for Novartis's material breach if such breach remains uncured for 60 days (such cure period shall be extended for an additional period during which Novartis is making good faith efforts to cure such breach) or (b) for Novartis's failure to use commercially reasonable efforts to develop or commercialize AL102 and/or the Novartis Licensed Product not remedied within four months following written notice to Novartis. Novartis has the right to terminate the Novartis Agreement (a) in its entirety or on a country-by-country basis for convenience, upon 60 days' written notice to us, (b) for our material breach if such breach remains uncured for 60 days (such cure period shall be extended for an additional period during which we are making good faith efforts to cure such breach) or (c) upon immediate written notice to us for insolvency-related events involving us.

Manufacturing

We rely on third parties to manufacture AL101 and AL102. We have entered into agreements with leading CMOs to produce both AL101 and AL102 for our ongoing and planned clinical studies and clinical trials for AL101 and AL102. We are also currently in the process of manufacturing batches to support all of our expected clinical supply needs as well as batches to support a potential New Drug Application, or NDA, submission. We require all of our contract manufacturing organizations, or CMOs, to conduct manufacturing activities in compliance with current good manufacturing practice, or cGMP, requirements. We currently rely solely on these CMOs for scale-up and process development work and to produce sufficient quantities of our product candidates for use in clinical trials. We anticipate that these CMOs will have the capacity to support both clinical supply and commercial-scale production, but we do not have any formal agreements at this time to cover commercial production. We may also elect to enter into agreements with other CMOs to manufacture supplies of drug substance and finished drug product.

Sales and Marketing

We intend to market and commercialize our product candidates, if approved, by building our own specialized sales and marketing organization initially in the United States. We believe our target market can be addressed by a small number of dedicated marketing and medical sales specialists covering specialized oncologists treating the target patient population. We may also selectively pursue strategic collaborations with third parties to maximize the commercial potential of our product candidates, if approved.

Competition

The pharmaceutical industry is characterized by rapid evolution of technologies and intense competition. While we believe that our product candidates, technology, knowledge, experience and scientific resources provide us with competitive advantages, we face competition from major pharmaceutical and biotechnology companies, academic institutions, governmental agencies and public and private research institutions, among others. Any product candidates that we successfully develop and commercialize will compete with approved treatment options, if any, including off-label therapies, and new therapies that may become available in the future. Key considerations that would impact our ability to effectively compete with other therapies include the efficacy, safety, method of administration, cost, level of promotional activity and intellectual property protection of our products. Many of the companies against which we may compete have significantly greater financial resources and expertise than we do in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals and marketing approved products.

We consider our most direct competitors with respect to AL101 and AL102 to be companies developing GSIs, including SpringWorks Therapeutics, Inc. and Celgene Corporation, recently acquired by BMS, or companies that are developing Notch inhibitors, including, but not limited to, Cellestia Biotech AG and Ciclomed LLC.

In addition, with respect to AL101 for the treatment of ACC, we are aware that other companies are, or may be, developing products for this indication, including, but not limited to, GlaxoSmithKline plc, Cellestia Biotech AG and Elevar Therapeutics, Inc., which we believe all are at an early development stage.

With respect to AL102, we are aware that other companies are, or may be, developing product candidates for the treatment of desmoid tumors, including, but not limited to, SpringWorks Therapeutics, Inc., Bayer Corporation, Cellestia Biotech AG and Iterion Therapeutics, Inc.

In addition, with respect to AL102 for the treatment of T-ALL, we are aware that other companies are, or may be, developing products for this indication, including, but not limited to, Sanofi S.A., Janssen Pharmaceutica, Jazz Pharmaceuticals plc and Vasgene Therapeutics, Inc

With respect to MM, we are aware that other companies are, or may be, developing product candidates with GSI as anti-BCMA agents, including, but not limited to, Springworks Therapeutics, Inc. in collaboration with GlaxoSmithKline plc, Janssen, Allogene, Pfizer, Precision Biosciences and Celgene Corporation, recently acquired by BMS.

Smaller or early-stage companies, including oncology-focused therapeutics companies, may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These companies may also compete with us in recruiting and retaining qualified scientific and management personnel, establishing clinical trial sites, enrolling patients in clinical trials and acquiring technologies complementary to, or necessary for, our programs.

The availability of reimbursement from government and private payors will also significantly impact the pricing and competitiveness of our products. Our competitors may obtain FDA or other regulatory approvals for their products more rapidly than we may obtain approvals for our product candidates, if any, which could result in our competitors establishing a strong market position before we are able to commercialize our product candidates.

Intellectual Property

Our success depends in part on our ability to obtain and maintain intellectual property and proprietary protection for our product candidates, manufacturing and process discoveries and other know-how, to operate without infringing, misappropriating or otherwise violating the intellectual property and proprietary rights of others, and to defend and enforce, and prevent others from infringing, misappropriating or otherwise violating, our intellectual property and proprietary rights. We take efforts to protect our proprietary position using a variety of methods, which include pursuit of U.S. and foreign patent applications related to our proprietary technology, inventions and improvements, such as compositions of matter and methods of use, that we determine are important to the development and implementation of our business. We also may rely on trade secrets, trademarks, know-how, continuing technological innovation and potential in-licensing opportunities to develop and maintain our proprietary position. For more information regarding risks relating to intellectual property, please see "Risk Factors—Risks Related to Our Intellectual Property."

Patents and Patent Applications

The term of individual patents depends upon the legal term of patents in the countries in which they are obtained. In most countries in which we file patent applications, including the United States, the patent term is generally 20 years from the earliest date of filing a non-provisional patent application, assuming the patent has not been terminally disclaimed over a commonly-owned patent or a patent naming a common inventor, or over a patent not commonly owned but that was disqualified as prior art as the result of activities undertaken within the scope of a joint research agreement. In the United States, the term of a patent may also be eligible for patent term adjustment for delays within the United States Patent and Trademark Office, or USPTO. In addition, for patents that cover an FDA-approved drug, the Drug Price Competition and Patent Term Restoration Act of 1984, or the Hatch-Waxman Act, may permit a patent term extension of up to five years beyond the expiration of the patent. While the length of such patent term extension is related to the length of time the drug is under regulatory review, patent term extension cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval, only one patent per approved drug may be extended and only those claims covering the approved drug product, a method for using it or a method for manufacturing it may be extended. Similar provisions are available in Europe and certain other foreign jurisdictions to extend the term of a patent that covers an approved drug. In the future, if and when our products receive FDA approval, we expect to apply for patent term extensions on patents covering those products. We plan to seek any available patent term extension to any issued patents we may be granted in any jurisdiction where such extensions are available; however, there is no guarantee that the applicable authorities, including the FDA and the USPTO in the United States, will agree with our assessment of whether such extensions should be granted, and if granted, the length of such extensions.

As of December 31, 2021, we owned or exclusively licensed a total of five issued U.S. patents, 124 granted foreign patents, nine pending U.S. patent applications, 69 pending foreign patent applications, and three pending Patent Cooperation Treaty, or PCT, applications.

In November 2017, we entered into the BMS License Agreement, pursuant to which we acquired exclusive worldwide rights under certain patents and know-how controlled by BMS to research, discover, develop, make, have made, use, sell, offer to sell, export, import and commercialize AL101 and AL102. For more information regarding the BMS License Agreement, please see "—License Agreements." As of December 31, 2021, the patent rights exclusively in-licensed under the BMS License Agreement include the following patent families:

- A patent family having claims directed to the composition of matter of AL101 and methods of treating certain types of cancer, which includes two issued U.S. patents, 64 granted patents in 64 foreign jurisdictions (including China, the European Patent Office, or EPO, Japan and the Russian Federation) and four pending patent applications in foreign jurisdictions. Without taking potential patent term extension or adjustment into account, the issued patents and any patents issued from pending applications in this family are expected to expire in 2032.

- A patent family having claims directed to the composition of matter of AL102 and methods of treating certain types of cancer, which includes two issued U.S. patents, 61 granted patents in 61 foreign jurisdictions (including China, the EPO, Japan and the Russian Federation), and six pending patent applications in six foreign jurisdictions. Without taking potential patent term extension or adjustment into account, the issued patents and any patents issued from pending applications in this family are expected to expire in 2033.

- A patent family consisting of one issued U.S. patent having claims directed to the method of use for the combination of AL101 with gemcitabine for treating cancer that is expected to expire, without taking potential patent term extension or adjustment into account, in 2034.

As of December 31, 2021, we solely owned 8 U.S. pending patent applications, two PCT application, and 47 foreign pending applications. In addition, we co-owned one U.S. pending application and 11 foreign pending applications with BMS, covering the use of AL101 for treating T-cell acute lymphoblastic leukemia (T-ALL) and for the use of AL102 for treating Desmoid tumors.

One of our solely-owned patent families, consisting of one pending U.S. patent application and 11 foreign pending applications, includes claims directed to methods of using AL101 to treat Notch-altered ACC.

Another solely-owned patent family, consisting of one pending U.S. patent application and 10 foreign pending applications, includes claims directed to methods of using AL101 to treat Notch-altered TNBC.

A third solely-owned patent family, consisting of one U.S. pending application and 12 foreign pending applications, includes claims directed to AL102 and BCMA-related combination treatments and methods of use for treating multiple myeloma. Any patents issued from our owned patent applications or from patent applications claiming the priority of such patent applications are expected to expire, without taking potential patent term extension or adjustment into account, between 2039 and 2040.

Trade Secrets

We also rely upon trade secrets, know-how, confidential information and continuing technological innovation to develop and maintain our competitive position, and seek to protect and maintain the confidentiality of such items to protect aspects of our business that are not amenable to, or that we do not presently consider appropriate for, patent protection. We maintain efforts to protect such proprietary rights through a variety of methods, including confidentiality agreements, invention assignment agreements, and non-solicitation and non-compete agreements with employees, consultants, collaborators, advisors, suppliers and other parties who may have access to our confidential or proprietary information. These agreements generally provide that all confidential information developed or made known to the other party during the course of its relationship with us is to be kept confidential and not disclosed to third parties except in specific circumstances. Where applicable, the agreements provide that all inventions to which the other party contributed as an inventor shall be assigned to us, and as such, will become our property. There can be no assurance, however, that these agreements will be self-executing or otherwise provide meaningful protection or adequate remedies for our trade secrets or other proprietary information, including in the event of unauthorized use or disclosure of such information. We also seek to preserve the integrity and confidentiality of our trade secrets 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 the measures we take to protect and preserve our trade secrets, such measures can be breached, and we may not have adequate remedies for any such breach. In addition, our trade secrets may otherwise become known or be independently discovered by competitors. For more information regarding risks relating to trade secrets, third parties and other factors that could affect our intellectual property rights, please see “Risk Factors—Risks Related to Our Intellectual Property.”

Government Regulation

Government authorities in the United States, at the federal, state and local level, and other countries extensively regulate, among other things, the research, development, testing, manufacture, quality control, approval, labeling, packaging, storage, record-keeping, promotion, advertising, distribution, marketing and export and import of products such as those we are developing. A new drug must be approved by the FDA through the NDA process before it may be legally marketed in the United States.

U.S. Drug Development Process

In the United States, the FDA regulates drugs under the federal Food, Drug, and Cosmetic Act, or the 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 require the expenditure of substantial time and financial resources.

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

- completion of preclinical laboratory tests, animal studies and formulation studies in accordance with FDA's good laboratory practice requirements and other applicable regulations;
- submission to the FDA of an investigational new drug application, or IND, which must become effective before human clinical trials may begin;
- approval by an independent institutional review board, or IRB, or ethics committee at each clinical site before each trial may be initiated;
- performance of adequate and well-controlled human clinical trials in accordance with good clinical practice requirements, or GCPs to establish the safety and efficacy of the proposed drug for its intended use;
- submission to the FDA of an NDA after completion of all pivotal trials;
- satisfactory completion of an FDA advisory committee review, if applicable;
- satisfactory completion of an FDA inspection of the manufacturing facility or facilities at which the drug is produced to assess compliance with cGMP requirements to assure that the facilities, methods and controls are adequate to preserve the drug's identity, strength, quality and purity, and of selected clinical investigation sites to assess compliance with GCPs; and
- FDA review and approval of the NDA to permit commercial marketing of the product for particular indications for use in the United States.

Prior to beginning the first clinical trial with a product candidate in the United States, we must submit an IND to the FDA. An IND is a request for authorization from the FDA to administer an investigational new drug product to humans. The central focus of an IND submission is on the general investigational plan and the protocol(s) for clinical studies. The IND also includes results of animal and *in vitro* studies assessing the toxicology, pharmacokinetics, pharmacology, and pharmacodynamics characteristics of the product; chemistry, manufacturing, and controls information; and any available human data or literature to support the use of the investigational product. An IND must become effective before human clinical trials may begin. The IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA, within the 30-day time period, raises safety concerns or questions about the proposed clinical trial. In such a case, the IND may be placed on clinical hold and the IND sponsor and the FDA must resolve any outstanding concerns or questions before the clinical trial can begin. Submission of an IND therefore may or may not result in FDA authorization to begin a clinical trial.

Clinical trials involve the administration of the investigational product to human subjects under the supervision of qualified investigators in accordance with GCPs, which include the requirement that all research subjects provide their informed consent for their participation in any clinical study. Clinical trials are conducted under protocols detailing, among other things, the objectives of the study, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated. A separate submission to the existing IND must be made for each successive clinical trial conducted during product development and for any subsequent protocol amendments. While the IND is active, progress reports summarizing the results of the clinical trials and nonclinical studies performed since the last progress report, among other information, must be submitted at least annually to the FDA, and written IND safety reports must be submitted to the FDA and investigators for serious and unexpected suspected adverse events, findings from other studies suggesting a significant risk to humans exposed to the drug, findings from animal or in vitro testing suggesting a significant risk to humans exposed to the drug, and any clinically important increased rate of a serious suspected adverse reaction compared to that listed in the protocol or investigator brochure.

Furthermore, an independent IRB for each site proposing to conduct the clinical trial must review and approve the plan for any clinical trial and its informed consent form before the clinical trial begins at that site and must monitor the study until completed. Regulatory authorities, the IRB or the sponsor may suspend a clinical trial at any time on various grounds, including a finding that the subjects are being exposed to an unacceptable health risk or that the trial is unlikely to meet its stated objectives. Some studies also include oversight by an independent group of qualified experts organized by the clinical study sponsor, known as a data safety monitoring board, which provides authorization for whether or not a study may move forward at designated check points based on access to certain data from the study and may halt the clinical trial if it determines that there is an unacceptable safety risk for subjects or other grounds, such as no demonstration of efficacy. There are also requirements governing the reporting of ongoing clinical studies and clinical study results to public registries.

Human clinical trials are typically conducted in three sequential phases that may overlap or be combined:

- *Phase 1:* The product candidate is initially introduced into healthy human subjects or patients with the target disease or condition. These studies are designed to test the safety, dosage tolerance, absorption, metabolism and distribution of the investigational product in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness. In the case of some products for severe or life-threatening diseases, such as cancer, especially when the product may be too inherently toxic to ethically administer to healthy volunteers, the initial human testing is often conducted in patients.

- *Phase 2:* The product candidate is administered to a limited patient population with a specified disease or condition to evaluate the preliminary efficacy, optimal dosages and dosing schedule and to identify possible adverse side effects and safety risks. Multiple Phase 2 clinical trials may be conducted to obtain information prior to beginning larger and more expensive Phase 3 clinical trials.

- *Phase 3:* The product candidate is administered to an expanded patient population to further evaluate dosage, to provide statistically significant evidence of clinical efficacy and to further test for safety, generally at multiple geographically dispersed clinical trial sites. These clinical trials are intended to establish the overall risk/benefit ratio of the investigational product and to provide an adequate basis for product approval.

Post-approval trials, sometimes referred to as Phase 4 studies, may be conducted after initial marketing approval. These trials are used to gain additional experience from the treatment of patients in the intended therapeutic indication. In certain instances, the FDA may mandate the performance of Phase 4 clinical trials as a condition of approval of an NDA.

During the development of a new drug, sponsors are given opportunities to meet with the FDA at certain points. These points may be prior to submission of an IND, at the end of Phase 2, and before an NDA is submitted. Meetings at other times may be requested. These meetings can provide an opportunity for the sponsor to share information about the data gathered to date, for the FDA to provide advice, and for the sponsor and the FDA to reach consensus on the next phase of development. Sponsors typically use the meetings at the end of the Phase 2 trial to discuss Phase 2 clinical results and present plans for the pivotal Phase 3 clinical trials that they believe will support approval of the new drug.

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

U.S. Review and Approval Process

Assuming successful completion of all required testing in accordance with all applicable regulatory requirements, the results of product development, preclinical and other non-clinical studies and clinical trials, along with descriptions of the manufacturing process, analytical tests conducted on the chemistry of the drug, proposed labeling and other relevant information are submitted to the FDA as part of an NDA requesting approval to market the product. The submission of an NDA is subject to the payment of substantial user fees; a waiver of such fees may be obtained under certain limited circumstances. Additionally, no user fees are assessed on NDAs for products designated as orphan drugs, unless the product also includes a non-orphan indication. 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 NDA must be resubmitted with the additional information. The resubmitted application also is subject to review before the FDA accepts it for filing. Once filed, the FDA reviews an NDA to determine, among other things, whether a product is safe and effective for its intended use and whether its manufacturing is cGMP-compliant to assure and preserve the product's identity, strength, quality and purity. 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 twelve months from the date the NDA is submitted to FDA because the FDA has approximately two months to make a "filing" decision after it the application is submitted.

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 will typically inspect the facility or facilities where the product is manufactured. The FDA will not approve an application unless it determines that the manufacturing processes and facilities are in compliance with cGMP and adequate to assure consistent production of the product within required specifications. Additionally, before approving a NDA, the FDA will typically inspect one or more clinical sites to assure compliance with GCPs.

After the FDA evaluates an NDA, it will issue an approval letter or a Complete Response Letter. An approval letter authorizes commercial marketing of the drug with prescribing information for specific indications. A Complete Response Letter indicates that the review cycle of the application is complete, and the application will not be approved in its present form. A Complete Response Letter usually describes the specific deficiencies in the NDA identified by the FDA and may require additional clinical data, such as an additional clinical or other significant and time-consuming requirements related to clinical trials, nonclinical studies or manufacturing. If a Complete Response Letter is issued, the sponsor must resubmit the NDA or, addressing all of the deficiencies identified in the letter, or withdraw the application. Even if such data and information are submitted, the FDA may decide that the NDA does not satisfy the criteria for approval.

If regulatory approval of a product is granted, such approval will be granted for particular indications and may entail limitations on the indicated uses for which such product may be marketed. For example, the FDA may approve the NDA with a Risk Evaluation and Mitigation Strategy, or REMS, to ensure the benefits of the product outweigh its risks. A REMS is a safety strategy to manage a known or potential serious risk associated with a medicine and to enable patients to have continued access to such medicines by managing their safe use, and could include medication guides, physician communication plans, or elements to assure safe use, such as restricted distribution methods, patient registries, and other risk minimization tools. The FDA also may condition approval on, among other things, changes to proposed labeling or the development of adequate controls and specifications. Once approved, the FDA may withdraw the product approval if compliance with pre- and post-marketing requirements is not maintained or if problems occur after the product reaches the marketplace. The FDA may also require one or more Phase 4 post-market studies and surveillance to further assess and monitor the product's safety and effectiveness after commercialization, and may limit further marketing of the product based on the results of these post-marketing studies.

In addition, the Pediatric Research Equity Act, or PREA, requires a sponsor to conduct pediatric clinical trials for most drugs, for a new active ingredient, new indication, new dosage form, new dosing regimen or new route of administration. Under PREA, original NDAs and supplements must contain a pediatric assessment unless the sponsor has received a deferral or waiver. The required assessment must evaluate the safety and effectiveness of the product for the claimed indications in all relevant pediatric subpopulations and support dosing and administration for each pediatric subpopulation for which the product is safe and effective. The sponsor or FDA may request a deferral of pediatric clinical trials for some or all of the pediatric subpopulations. A deferral may be granted for several reasons, including a finding that the drug is ready for approval for use in adults before pediatric clinical trials are complete or that additional safety or effectiveness data need to be collected before the pediatric clinical trials begin. The FDA must send a non-compliance letter to any sponsor that fails to submit the required assessment, keep a deferral current or fails to submit a request for approval of a pediatric formulation.

Orphan Drug Designation

Under the Orphan Drug Act, the FDA may grant orphan 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 individuals in the United States, there is no reasonable expectation that the cost of developing and making a drug product available in the United States for this type of disease or condition will be recovered from sales of the product. Orphan designation must be requested before submitting an NDA. After the FDA grants orphan designation, the identity of the therapeutic agent and its potential orphan use are disclosed publicly by the FDA. Orphan designation does not convey any advantage in or shorten the duration of the regulatory review and approval process.

If a product that has orphan designation subsequently receives the first FDA approval for the disease or condition for which it has such designation, the product is entitled to orphan product exclusivity, which means that the FDA may not approve any other applications to market the same drug for the same disease or condition for seven years, except in limited circumstances, such as a showing of clinical superiority to the product with orphan exclusivity or inability to manufacture the product in sufficient quantities. The designation of such drug also entitles a party to financial incentives such as opportunities for grant funding towards clinical trial costs, tax advantages and user-fee waivers. However, competitors, may receive approval of different products for the indication for which the orphan product has exclusivity or obtain approval for the same product but for a different indication for which the orphan product has exclusivity. Orphan exclusivity also could block the approval of a competing product candidate for seven years if a competitor obtains approval of the same drug as defined by the FDA or if such product candidate is determined to be contained within the competitor's product for the same indication or disease. In addition, if an orphan designated product receives marketing approval for an indication broader than what is designated, it may not be entitled to orphan exclusivity.

Expedited Development and Review Programs

The FDA offers a number of expedited development and review programs for qualifying product candidates. For example, the FDA has a fast track designation program that is intended to expedite or facilitate the process for reviewing drug products that meet certain criteria. Specifically, drugs are eligible for fast track designation if they are intended to treat a serious or life-threatening disease or condition and demonstrate the potential to address unmet medical needs for the disease or condition. Fast track designation applies to the combination of the product candidate and the specific indication for which it is being studied. The sponsor of a fast track product candidate has opportunities for more frequent interactions with the applicable FDA review team during product development and, once an NDA is submitted, the application may be eligible for priority review. With regard to a fast track product candidate, the FDA may consider for review sections of the NDA on a rolling basis before the complete application is submitted, 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.

A product candidate intended to treat a serious or life-threatening disease or condition may also be eligible for breakthrough therapy designation to expedite its development and review. A product candidate can receive breakthrough therapy designation if preliminary clinical evidence indicates that the product candidate, alone or in combination with one or more other drugs or biologics, 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 designation includes all of the fast track program features, as well as more intensive FDA interaction and guidance beginning as early as Phase 1 and an organizational commitment to expedite the development and review of the product candidate, including involvement of senior managers.

Any product candidate submitted to the FDA for approval, including a product candidate with a fast track or breakthrough therapy designation, may also be eligible for other types of FDA programs intended to expedite development and review, such as priority review and accelerated approval. An NDA is eligible for priority review if the product candidate has the potential to provide a significant improvement in the treatment, diagnosis or prevention of a disease compared to available products. The FDA will attempt to direct additional resources to the evaluation of an application for a product candidate designated for priority review in an effort to facilitate the review. The FDA endeavors to review applications with priority review designations within six months of the filing date as compared to ten months for review of new molecular entity NDAs under its current PDUFA review goals.

In addition, a product candidate may be eligible for accelerated approval. Product candidates intended to treat serious or life-threatening diseases or conditions may be eligible for accelerated approval upon a determination that the product candidate 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 will generally require that a sponsor of a drug receiving accelerated approval to perform adequate and well-controlled post-marketing clinical trials to verify and describe the anticipated effect on irreversible morbidity or mortality or other clinical benefit. Products receiving accelerated approval may be subject to expedited withdrawal procedures if the sponsor fails to conduct the required post-marketing studies or if such studies fail to verify the predicted clinical benefit. In addition, the FDA currently requires pre-approval of promotional materials as a condition for accelerated approval, which could adversely impact the timing of the commercial launch of the product.

Fast track designation, breakthrough therapy designation, priority review and accelerated approval do not change the standards for approval but may expedite the development or approval process. 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.

Post-Approval Requirements

Any products manufactured or distributed pursuant to FDA approvals are subject to pervasive and continuing regulation by the FDA, including, among other things, requirements relating to record-keeping, reporting of adverse experiences, periodic reporting, product sampling and distribution, and advertising and promotion of the product. After approval, most changes to the approved product, such as adding new indications or other labeling claims, are subject to prior FDA review and approval. There also are continuing, annual program fees for any marketed products. Drug manufacturers and their subcontractors are required to register their establishments with the FDA and certain state agencies, and are subject to periodic unannounced inspections by the FDA and certain state agencies for compliance with cGMP, which impose certain procedural and documentation requirements upon NDA sponsors and any third-party manufacturers. Changes to the manufacturing process are strictly regulated, and, depending on the significance of the change, may require prior FDA approval before being implemented. FDA regulations also require investigation and correction of any deviations from cGMP and impose reporting requirements upon us and any third-party manufacturers that we 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 aspects of regulatory compliance.

The FDA may withdraw 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, or with manufacturing processes, or failure to comply with regulatory requirements, may result in revisions to the approved labeling to add new safety information; imposition of post-market studies or clinical studies to assess new safety risks; or imposition of distribution restrictions 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 untitled letters;
- clinical holds on clinical studies;
- refusal of the FDA to approve pending applications or supplements to approved applications, or suspension or revocation of product license approvals;
- product seizure or detention, or refusal to permit the import or export of products;
- consent decrees, corporate integrity agreements, debarment or exclusion from federal healthcare programs;
- mandated modification of promotional materials and labeling and the issuance of corrective information;

- the issuance of safety alerts, Dear Healthcare Provider letters, press releases and other communications containing warnings or other safety information about the product; or

- injunctions or the imposition of civil or criminal penalties.

The FDA closely regulates the marketing, labeling, advertising and promotion of drug products. A company can make only those claims relating to safety and efficacy, purity and potency that are approved by the FDA and in accordance with the provisions of the approved label. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses. Failure to comply with these requirements can result in, among other things, adverse publicity, warning letters, corrective advertising and potential civil and criminal penalties. Physicians may prescribe legally available products for uses that are not described in the product's labeling and that differ from those tested by us and approved by the FDA. Such off-label uses are common across medical specialties. Physicians may believe that such off-label uses are the best treatment for many patients in varied circumstances. The FDA does not regulate the behavior of physicians in their choice of treatments. The FDA does, however, restrict manufacturer's communications on the subject of off-label use of their products.

Marketing Exclusivity

Market exclusivity provisions authorized under the FDCA can delay the submission or the approval of certain marketing applications. The FDCA provides a five-year period of non-patent marketing exclusivity within the United States to the first applicant to obtain approval of an NDA for a new chemical entity. A drug is a new chemical entity if the FDA has not previously approved any other new drug containing the same active moiety, which is the molecule or ion responsible for the action of the drug substance. During the exclusivity period, the FDA may not approve or even accept for review an abbreviated new drug application, or ANDA, or an NDA submitted under Section 505(b)(2), or 505(b)(2) NDA, submitted by another company for another drug based on the same active moiety, regardless of whether the drug is intended for the same indication as the original innovative drug or for another indication, where the applicant does not own or have a legal right of reference to all the data required for approval. However, an application may be submitted after four years if it contains a certification of patent invalidity or non-infringement to one of the patents listed with the FDA by the innovator NDA holder.

The FDCA alternatively provides three years of marketing exclusivity for an NDA, or supplement to an existing NDA if new clinical investigations, other than bioavailability studies, that were conducted or sponsored by the applicant are deemed by the FDA to be essential to the approval of the application, for example new indications, dosages or strengths of an existing drug. This three-year exclusivity covers only the modification for which the drug received approval on the basis of the new clinical investigations and does not prohibit the FDA from approving ANDAs or 505(b)(2) NDAs for drugs containing the active agent for the original indication or condition of use. Five-year and three-year exclusivity will not delay the submission or approval of a full NDA. However, an applicant submitting a full NDA would be required to conduct or obtain a right of reference to any preclinical studies and adequate and well-controlled clinical trials necessary to demonstrate safety and effectiveness.

Pediatric exclusivity is another type of marketing exclusivity available in the United States. Pediatric exclusivity provides for an additional six months of marketing exclusivity attached to another period of exclusivity if a sponsor conducts clinical trials in children in response to a written request from the FDA. The issuance of a written request does not require the sponsor to undertake the described clinical trials. In addition, orphan drug exclusivity, as described above, may offer a seven-year period of marketing exclusivity, except in certain circumstances.

FDA Regulation of Companion Diagnostics

We expect that certain of our product candidates may require an in vitro diagnostic to identify appropriate patient populations for our product candidates. These diagnostics, often referred to as companion diagnostics, are regulated as medical devices. In the United States, the FDCA and its implementing regulations, and other federal and state statutes and regulations govern, among other things, medical device design and development, preclinical and clinical testing, premarket clearance or approval, registration and listing, manufacturing, labeling, storage, advertising and promotion, sales and distribution, export and import, and post-market surveillance. Unless an exemption applies, diagnostic tests require marketing clearance or approval from the FDA prior to commercial distribution. The two primary types of FDA marketing authorization applicable to a medical device are premarket notification, also called 510(k) clearance, and premarket approval, or PMA approval. We expect that any companion diagnostic developed for our product candidates will utilize the PMA pathway.

If use of companion diagnostic is essential to safe and effective use of a drug or biologic product, then the FDA generally will require approval or clearance of the diagnostic contemporaneously with the approval of the therapeutic product. On August 6, 2014, the FDA issued a final guidance document addressing the development and approval process for "In Vitro Companion Diagnostic Devices." According to the guidance, for novel product candidates, a companion diagnostic device and its corresponding drug candidate should be approved or cleared contemporaneously by FDA for the use indicated in the therapeutic product labeling. The guidance also explains that a companion diagnostic device used to make treatment decisions in clinical trials of a drug generally will be considered an investigational device, unless it is employed for an intended use for which the device is already approved or cleared. If used to make critical treatment decisions, such as patient selection, the diagnostic device generally will be considered a significant risk device under the FDA's Investigational Device Exemption, or IDE, regulations. Thus, the sponsor of the diagnostic device will be required to comply with the IDE regulations. According to the guidance, if a diagnostic device and a drug are to be studied together to support their respective approvals, both products can be studied in the same investigational study, if the study meets both the requirements of the IDE regulations and the IND regulations. The guidance provides that depending on the details of the study plan and subjects, a sponsor may seek to submit an IND alone, or both an IND and an IDE.

The FDA has generally required companion diagnostics intended to select the patients who will respond to cancer treatment to obtain approval of a PMA for that diagnostic simultaneously with approval of the therapeutic. The PMA process, including the gathering of clinical and preclinical data and the submission to and review by the FDA, can take several years or longer. It involves a rigorous premarket review during which the applicant must prepare and provide the FDA with reasonable assurance of the device's safety and effectiveness and information about the device and its components regarding, among other things, device design, manufacturing and labeling. In addition, PMAs for certain devices must generally include the results from extensive preclinical and adequate and well-controlled clinical trials to establish the safety and effectiveness of the device for each indication for which FDA approval is sought. In particular, for a diagnostic, the applicant must demonstrate that the diagnostic produces reproducible results when the same sample is tested multiple times by multiple users at multiple laboratories. As part of the PMA review, the FDA will typically inspect the manufacturer's facilities for compliance with the Quality System Regulation, or QSR, which imposes elaborate testing, control, documentation and other quality assurance requirements.

If the FDA evaluations of both the PMA application and the manufacturing facilities are favorable, the FDA will either issue an approval letter or an approvable letter, which usually contains a number of conditions that must be met in order to secure the final approval of the PMA, such as changes in labeling, or specific additional information, such as submission of final labeling, in order to secure final approval of the PMA. If the FDA concludes that the applicable criteria have been met, the FDA will issue a PMA for the approved indications, which can be more limited than those originally sought by the applicant. The PMA can include post-approval conditions that the FDA believes necessary to ensure the safety and effectiveness of the device, including, among other things, restrictions on labeling, promotion, sale and distribution.

If the FDA's evaluation of the PMA or manufacturing facilities is not favorable, the FDA will deny approval of the PMA or issue a not approvable letter. A not approvable letter will outline the deficiencies in the application and, where practical, will identify what is necessary to make the PMA approvable. The FDA may also determine that additional clinical trials are necessary, in which case the PMA approval may be delayed for several months or years while the trials are conducted and then the data submitted in an amendment to the PMA. Once granted, PMA approval may be withdrawn by the FDA if compliance with post approval requirements, conditions of approval or other regulatory standards is not maintained or problems are identified following initial marketing. PMA approval is not guaranteed, and the FDA may ultimately respond to a PMA submission with a not approvable determination based on deficiencies in the application and require additional clinical trial or other data that may be expensive and time-consuming to generate and that can substantially delay approval.

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

Foreign Government Regulation

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 products. The foreign regulatory approval process includes all of the risks associated with FDA approval, as well as additional country-specific regulation

Whether or not we obtain FDA approval for a product candidate, we must obtain the requisite approvals from regulatory authorities in foreign countries prior to the commencement of clinical trials or marketing of the product in those countries. The requirements and process governing the conduct of clinical trials, approval process, product licensing, pricing and reimbursement vary from country to country. Failure to comply with applicable foreign regulatory requirements, may be subject to, among other things, fines, suspension or withdrawal of regulatory approvals, product recalls, seizure of products, operating restrictions and criminal prosecution.

Non-clinical studies and clinical trials

Similarly to the United States, the various phases of non-clinical and clinical research in the European Union, or EU, are subject to significant regulatory controls.

Non-clinical studies are performed to demonstrate the health or environmental safety of new chemical or biological substances. Non-clinical studies must be conducted in compliance with the principles of good laboratory practice, or GLP, as set forth in EU Directive 2004/10/EC. In particular, non-clinical studies, both in vitro and in vivo, must be planned, performed, monitored, recorded, reported and archived in accordance with the GLP principles, which define a set of rules and criteria for a quality system for the organizational process and the conditions for non-clinical studies. These GLP standards reflect the Organization for Economic Co-operation and Development requirements.

Clinical trials of medicinal products in the EU must be conducted in accordance with EU and national regulations and the International Conference on Harmonization, or ICH, guidelines on Good Clinical Practices, or GCP, as well as the applicable regulatory requirements and the ethical principles that have their origin in the Declaration of Helsinki. If the sponsor of the clinical trial is not established within the EU, it must appoint an EU entity to act as its legal representative. The sponsor must take out a clinical trial insurance policy, and in most EU member states, the sponsor is liable to provide 'no fault' compensation to any study subject injured in the clinical trial.

The regulatory landscape related to clinical trials in the EU has been subject to recent changes. The EU Clinical Trials Regulation, or CTR, which was adopted in April 2014 and repeals the EU Clinical Trials Directive, became applicable on January 31, 2022. Unlike directives, the CTR is directly applicable in all EU member states without the need for member states to further implement it into national law. The CTR notably harmonizes the assessment and supervision processes for clinical trials throughout the EU via a Clinical Trials Information System, which contains a centralized EU portal and database.

While the Clinical Trials Directive required a separate clinical trial application, or CTA, to be submitted in each member state, to both the competent national health authority and an independent ethics committee, much like the FDA and IRB respectively, the CTR introduces a centralized process and only requires the submission of a single application to all member states concerned. The CTR allows sponsors to make a single submission to both the competent authority and an ethics committee in each member state, leading to a single decision per member state. The CTA must include, among other things, a copy of the trial protocol and an investigational medicinal product dossier containing information about the manufacture and quality of the medicinal product under investigation. The assessment procedure of the CTA has been harmonized as well, including a joint assessment by all member states concerned, and a separate assessment by each member state with respect to specific requirements related to its own territory, including ethics rules. Each member state's decision is communicated to the sponsor via the centralized EU portal. Once the CTA is approved, clinical study development may proceed.

The CTR foresees a three-year transition period. The extent to which ongoing and new clinical trials will be governed by the CTR varies. For clinical trials whose CTA was made under the Clinical Trials Directive before January 31, 2022, the Clinical Trials Directive will continue to apply on a transitional basis for three years. Additionally, sponsors may still choose to submit a CTA under either the Clinical Trials Directive or the CTR until January 31, 2023 and, if authorized, those will be governed by the Clinical Trials Directive until January 31, 2025. By that date, all ongoing trials will become subject to the provisions of the CTR.

Medicines used in clinical trials must be manufactured in accordance with Good Manufacturing Practice , or GMP. Other national and EU-wide regulatory requirements may also apply.

Marketing Authorization

In order to market our future product candidates in the EU and many other foreign jurisdictions, we must obtain separate regulatory approvals. More concretely, in the EU, medicinal product candidates can only be commercialized after obtaining a marketing authorization, or MA. To obtain regulatory approval of a product candidate under EU regulatory systems, we must submit a MA application, or MAA. The process for doing this depends, among other things, on the nature of the medicinal product. There are two types of MAs:

- "Centralized MA" are issued by the European Commission through the centralized procedure, based on the opinion of the Committee for Medicinal Product for Human Use, or CHMP, of the European Medicines Agency, or EMA, and are valid throughout the EU. The centralized procedure is mandatory for certain types of product candidates, such as: (i) medicinal products derived from biotechnology processes, such as genetic engineering, (ii) designated orphan medicines, (iii) medicinal products containing a new active substance indicated for the treatment of certain diseases, such as HIV/AIDS, cancer, neurodegenerative diseases, diabetes, auto-immune and other immune dysfunctions and viral diseases and (iv) advanced therapy medicinal products, or ATMPs, such as gene therapy, somatic cell therapy or tissue-engineered medicines. The centralized procedure is optional for product candidates containing a new active substance not yet authorized in the EU, or for product candidates that constitute a significant therapeutic, scientific or technical innovation or which are in the interest of public health in the EU.

- "National MAs" are issued by the competent authorities of the EU member states, only cover their respective territory, and are available for product candidates not falling within the mandatory scope of the centralized procedure. Where a product has already been authorized for marketing in an EU member state, this national MA can be recognized in another member state through the mutual recognition procedure. If the product has not received a national MA in any member state at the time of application, it can be approved simultaneously in various member states through the decentralized procedure. Under the decentralized procedure an identical dossier is submitted to the competent authorities of each of the member states in which the MA is sought, one of which is selected by the applicant as the reference member state.

Under the centralized procedure the maximum timeframe for the evaluation of a MAA by the EMA is 210 days.

MAs have an initial duration of five years. After these five years, the authorization may be renewed for an unlimited period on the basis of a reevaluation of the risk-benefit balance.

Data and marketing exclusivity

The EU also provides opportunities for market exclusivity. Upon receiving MA, reference products generally receive eight years of data exclusivity and an additional two years of market exclusivity. If granted, the data exclusivity period prevents generic or biosimilar applicants from relying on the pre-clinical and clinical trial data contained in the dossier of the reference product when applying for a generic or biosimilar MA in the EU during a period of eight years from the date on which the reference product was first authorized in the EU. The market exclusivity period prevents a successful generic or biosimilar applicant from commercializing its product in the EU until 10 years have elapsed from the initial MA of the reference product in the EU. The overall 10-year market exclusivity period can be extended to a maximum of eleven years if, during the first eight years of those 10 years, the MA holder obtains an authorization for one or more new therapeutic indications which, during the scientific evaluation prior to their authorization, are held to bring a significant clinical benefit in comparison with existing therapies. However, there is no guarantee that a product will be considered by the EU's regulatory authorities to be a new chemical entity, and products may not qualify for data exclusivity.

The aforementioned EU rules are generally applicable in the European Economic Area, or EEA, which consists of the 27 EU member states plus Norway, Liechtenstein and Iceland.

Failure to comply with EU and member state laws that apply to the conduct of clinical trials, manufacturing approval, MA of medicinal products and marketing of such products, both before and after grant of the MA, manufacturing of pharmaceutical products, statutory health insurance, bribery and anti-corruption or with other applicable regulatory requirements may result in administrative, civil or criminal penalties. These penalties could include delays or refusal to authorize the conduct of clinical trials, or to grant MA, product withdrawals and recalls, product seizures, suspension, withdrawal or variation of the MA, total or partial suspension of production, distribution, manufacturing or clinical trials, operating restrictions, injunctions, suspension of licenses, fines and criminal penalties.

Brexit and the Regulatory Framework in the United Kingdom

The United Kingdom, or UK, left the EU on January 31, 2020, following which existing EU medicinal product legislation continued to apply in the UK during the transition period under the terms of the EU-UK Withdrawal Agreement. The transition period, which ended on December 31, 2020, maintained access to the EU single market and to the global trade deals negotiated by the EU on behalf of its members. The transition period provided time for the UK and EU to negotiate a framework for partnership for the future, which was then crystallized in the Trade and Cooperation Agreement, or TCA, and became effective on the January 1, 2021. The TCA includes specific provisions concerning pharmaceuticals, which include the mutual recognition of GMP inspections of manufacturing facilities for medicinal products and GMP documents issued, but does not foresee wholesale mutual recognition of UK and EU pharmaceutical regulations.

EU laws which have been transposed into UK law through secondary legislation continue to be applicable as “retained EU law”. However, new legislation such as the EU CTR will not be applicable. The UK government has passed a new Medicines and Medical Devices Act 2021, which introduces delegated powers in favor of the Secretary of State or an ‘appropriate authority’ to amend or supplement existing regulations in the area of medicinal products and medical devices. This allows new rules to be introduced in the future by way of secondary legislation, which aims to allow flexibility in addressing regulatory gaps and future changes in the fields of human medicines, clinical trials and medical devices.

As of January 1, 2021, the Medicines and Healthcare products Regulatory Agency, or MHRA, is the UK’s standalone medicines and medical devices regulator. As a result of the Northern Ireland protocol, different rules will apply in Northern Ireland than in England, Wales, and Scotland, together, Great Britain, or GB. Broadly, Northern Ireland will continue to follow the EU regulatory regime, but its national competent authority will remain the MHRA. The MHRA has published a guidance on how various aspects of the UK regulatory regime for medicines will operate in GB and in Northern Ireland following the expiry of the Brexit transition period on December 31, 2020. The guidance includes clinical trials, importing, exporting, and pharmacovigilance and is relevant to any business involved in the research, development, or commercialization of medicines in the UK. The new guidance was given effect via the Human Medicines Regulations (Amendment etc.) (EU Exit) Regulations 2019, or the Exit Regulations.

Regulation of Companion Diagnostics in the EU

In the EU, in vitro diagnostic medical devices, or IVD MDs, are regulated by Directive 98/79/EC, or IVDD, which regulates the placing on the market, the CE marking, the essential requirements, the conformity assessment procedures, the registration obligations for manufactures and devices as well as the vigilance procedure. In vitro diagnostic medical devices must comply with the requirements provided for in the Directive, and with further requirements implemented at national level (as the case may be).

The regulation of companion diagnostics will be subject to further requirements once the in-vitro diagnostic medical devices Regulation (No 2017/746), or IVDR, will become applicable on May 26, 2022. However on October 14, 2021, the European Commission proposed a “progressive” roll-out of the IVDR to prevent disruption in the supply of IVD MDs. The European Parliament and Council voted to adopt the proposed regulation on December 15, 2021 and the regulation entered into force on January 2022. The IVDR will fully apply on May 26, 2022 but there will be a tiered system extending the grace period for many devices (depending on their risk classification) before they have to be fully compliant with the regulation.

The IVDR introduces a new classification system for companion diagnostics which are now specifically defined as diagnostic tests that support the safe and effective use of a specific medicinal product, by identifying patients that are suitable or unsuitable for treatment. Companion diagnostics will have to undergo a conformity assessment by a notified body. Before it can issue a CE certificate, the notified body must seek a scientific opinion from the EMA on the suitability of the companion diagnostic to the medicinal product concerned if the medicinal product falls exclusively within the scope of the centralized procedure for the authorization of medicines, or the medicinal product is already authorized through the centralized procedure, or a MAA for the medicinal product has been submitted through the centralized procedure. For other substances, the notified body can seek the opinion from a national competent authorities or the EMA.

The aforementioned EU rules are generally applicable in the EEA.

Other Healthcare Laws

Pharmaceutical companies are subject to additional healthcare regulation and enforcement by the federal government and by authorities in the states and foreign jurisdictions in which they conduct their business. Such laws include, without limitation, U.S. federal and state anti-kickback, fraud and abuse, false claims, consumer fraud, pricing reporting, and transparency laws and regulations with respect to payments and other transfers of value made to physicians and other healthcare providers, as well as similar foreign laws in jurisdictions outside the U.S.

For example, the federal Anti-Kickback Statute prohibits, among other things, individuals or entities from knowingly and willfully offering, paying, soliciting or receiving remuneration, directly or indirectly, overtly or covertly, in cash or in kind 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. 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 civil False Claims Act and the civil monetary penalties statute. The federal civil and criminal false claims laws, including the civil False Claims Act, prohibit, among other things, any individual or entity from 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. The federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, created additional federal civil and criminal statutes that prohibit, among other things, knowingly and willfully executing a scheme to defraud any healthcare benefit program. Similar to the U.S. federal Anti-Kickback Statute, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation. 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 CMS information related to payments or other transfers of value made to physicians, certain other healthcare professionals, teaching hospitals, and applicable manufacturers and group purchasing organizations as well as ownership and investment interests held by physicians and their immediate family members. Additional reporting and transparency requirements for payments to physician assistants, nurse practitioners, clinical nurse specialists, certified registered nurse anesthetists, anesthesiology assistants and certified nurse midwives go into effect in 2022 for payments made in 2021.

Violation of any of such laws or any other governmental regulations that apply may result in penalties, including, without limitation, civil and criminal penalties, damages, fines, additional reporting obligations to resolve allegations of non-compliance, the curtailment or restructuring of operations, exclusion from participation in governmental healthcare programs and individual imprisonment.

Data Privacy and Security Laws

Numerous state, federal and foreign laws, regulations and standards govern the collection, use, access to, confidentiality and security of health-related and other personal information, and could apply now or in the future to our operations or the operations of our partners. In the United States, federal and state laws and regulations, including data breach notification laws, health information privacy and security laws and consumer protection laws and regulations govern the collection, use, disclosure, and protection of health-related and other personal information. In addition, certain foreign laws govern the privacy and security of personal data, including health-related data. Privacy and security laws, regulations, and other obligations are constantly evolving, may conflict with each other to complicate compliance efforts, and can result in investigations, proceedings, or actions that lead to significant civil and/or criminal penalties and restrictions on data processing.

Coverage and Reimbursement

Sales of any pharmaceutical product depend, in part, on the extent to which such product will be covered by third-party payors, such as federal, state and foreign government healthcare programs, commercial insurance and managed healthcare organizations, and the level of reimbursement for such product by third-party payors. Significant uncertainty exists as to the coverage and reimbursement status of any newly approved product. Decisions regarding the extent of coverage and amount of reimbursement to be provided are made on a plan-by-plan basis. One third-party payor's decision to cover a particular product does not ensure that other payors will also provide coverage for the product. As a result, the coverage determination process can require manufacturers to provide scientific and clinical support for the use of a product to each payor separately and can be a time-consuming process, with no assurance that coverage and adequate reimbursement will be applied consistently or obtained in the first instance.

In addition, third-party payors are increasingly reducing reimbursements for pharmaceutical products and services. The U.S. government and state legislatures have continued implementing cost-containment programs, including price controls, restrictions on coverage and reimbursement and requirements for substitution of generic products. Third-party payors are more and more challenging the prices charged, examining the medical necessity and reviewing the cost effectiveness of pharmaceutical products, in addition to questioning their safety and efficacy. Adoption of price controls and cost-containment measures, and adoption of more restrictive policies in jurisdictions with existing controls and measures, could further limit sales of any product. Decreases in third-party reimbursement for any product or a decision by a third-party payor not to cover a product could reduce physician usage and patient demand for the product.

In international markets, reimbursement and healthcare payment systems vary significantly by country, and many countries have instituted price ceilings on specific products and therapies. For example, the EU provides options for its member states to restrict the range of medicinal products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. A member state may approve a specific price for the medicinal product or it may instead adopt a system of direct or indirect controls on the profitability of the company placing the medicinal product on the market. Pharmaceutical products may face competition from lower-priced products in foreign countries that have placed price controls on pharmaceutical products and may also compete with imported foreign products. Furthermore, there is no assurance that a product will be considered medically reasonable and necessary for a specific indication, will be considered cost-effective by third-party payors, that an adequate level of reimbursement will be established even if coverage is available or that the third-party payors' reimbursement policies will not adversely affect the ability for manufacturers to sell products profitably.

Healthcare Reform

In the United States and certain foreign jurisdictions, there have been, and we expect there will continue to be, a number of legislative and regulatory changes to the healthcare system. In March 2010, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, or collectively, the ACA, was signed into law, which substantially changed the way healthcare is financed by both governmental and private insurers in the United States. The ACA contains a number of provisions, including those governing enrollment in federal healthcare programs, reimbursement adjustments and fraud and abuse changes. Additionally, the ACA increased the minimum level of Medicaid rebates payable by manufacturers of brand name drugs from 15.1% to 23.1% of the average manufacturer price; required collection of rebates for drugs paid by Medicaid managed care organizations; imposed a non-deductible annual fee on pharmaceutical manufacturers or importers who sell certain "branded prescription drugs" to specified federal government programs; expanded eligibility criteria for Medicaid programs; created a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research; and established a Center for Medicare & Medicaid Innovation at CMS to test innovative payment and service delivery models to lower Medicare and Medicaid spending, potentially including prescription drug spending.

Since its enactment, there have been judicial, executive and Congressional challenges to certain aspects of the ACA. On June 17, 2021, the U.S. Supreme Court dismissed the most recent judicial challenge to the ACA without specifically ruling on the constitutionality of the ACA. Prior to the Supreme Court's decision, President Biden issued an executive order initiating a special enrollment period from February 15, 2021 through August 15, 2021 for purposes of obtaining health insurance coverage through the ACA marketplace. The executive order also instructed certain governmental agencies to review and reconsider their existing policies and rules that limit access to healthcare.

Other legislative changes have been proposed and adopted since the ACA was enacted, including aggregate reductions of Medicare payments to providers of 2% per fiscal year and reduced payments to several types of Medicare providers, which will remain in effect through 2030, with the exception of a temporary suspension from May 1, 2020 through March 31, 2022 and a 1% reduction from April 1, 2022 through June 30, 2022, absent additional congressional action. More recently, on March 11, 2021, President Biden signed the American Rescue Plan Act of 2021 into law, which eliminates the statutory Medicaid drug rebate cap, currently set at 100% of a drug's average manufacturer price, beginning January 1, 2024.

We expect additional state, federal and foreign healthcare reform measures to be adopted in the future, any of which could limit the amounts that federal, state and foreign governments will pay for health products, which could result in reduced demand for our products, if approved or additional pricing pressure.

For instance, in December 2021, the EU Regulation No 2021/2282 on Health Technology Assessment, or HTA, amending Directive 2011/24/EU, was adopted. This regulation which entered into force in January 2022 intends to boost cooperation among EU member states in assessing health technologies, including some medical devices, and providing the basis for cooperation at the EU level for joint clinical assessments in these areas. The regulation foresees a three-year transitional period and will permit EU member states to use common HTA tools, methodologies, and procedures across the EU, working together in four main areas, including joint clinical assessment of the innovative health technologies with the most potential impact for patients, joint scientific consultations whereby developers can seek advice from HTA authorities, identification of emerging health technologies to identify promising technologies early, and continuing voluntary cooperation in other areas. Individual EU member states will continue to be responsible for assessing non-clinical (e.g., economic, social, ethical) aspects of health technologies, and making decisions on pricing and reimbursement.

Employees

As of December 31, 2021, we had 35 employees, including 10 employees with M.D. or Ph.D. degrees. Of these employees, 29 employees are engaged in research and development activities. None of our employees is represented by a labor union or covered by a collective bargaining agreement.

Corporate Information

We were incorporated in Delaware in November 2017. Our offices are located at Oppenheimer 4, Rehovot, Israel 76701014. Our common stock is listed on The Nasdaq Global Market under the symbol "AYLA."

Available Information

Our internet website address is www.ayalapharma.com. In addition to the information about us and our subsidiaries contained in this Annual Report on Form 10-K, information about us can be found on our website. Our website and information included in or linked to our website are not part of this Annual Report on Form 10-K.

Our annual reports on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K and amendments to those reports filed or furnished pursuant to Section 13(a) or 15(d) of the Securities Exchange Act of 1934, as amended, are available free of charge through our website as soon as reasonably practicable after they are electronically filed with or furnished to the Securities and Exchange Commission, or SEC. Additionally the SEC maintains an internet site that contains reports, proxy and information statements and other information. The address of the SEC's website is www.sec.gov.

Item 1A. Risk Factors.

You should carefully consider the risks and uncertainties described below and the other information Annual Report on Form 10-K before making an investment in our common stock. Our business, financial condition, results of operations, or prospects could be materially and adversely affected if any of these risks occurs, and as a result, the market price of our common stock could decline and you could lose all or part of your investment. This Annual Report on Form 10-K also contains forward-looking statements that involve risks and uncertainties. See "Special Note Regarding Forward-Looking Statements." Our actual results could differ materially and adversely from those anticipated in these forward-looking statements as a result of certain factors, including those set forth below.

Risks Related to Our Financial Position and Need for Additional Capital

We have incurred significant losses since inception and anticipate that we will continue to incur losses for the foreseeable future. We are not currently profitable, and we may never achieve or sustain profitability. If we are unable to achieve or sustain profitability, the market value of our common stock will likely decline.

We are a clinical-stage biopharmaceutical company with a limited operating history and have incurred significant losses since our formation. We had a net loss of approximately $40.3 million and $30.1 million for the years ended December 31, 2021 and 2020, respectively. As of December 31, 2021, we had an accumulated deficit of $111.1 million. As noted below, we have identified conditions and events that raise substantial doubt about our ability to continue as a going concern. We have not commercialized any products and have never generated revenue from the commercialization of any product. To date, we have devoted most of our financial resources to licensing product candidates and research and development, including our preclinical development activities and clinical trials.

We expect to incur significant operating expenses and increasing net losses for the next several years, at least, as we advance AL101, AL102 and any future product candidate through preclinical and clinical development, seek regulatory approvals and commercialize AL101, AL102 or any other product candidate, if approved. The costs of advancing product candidates into each clinical phase tend to increase substantially over the duration of the clinical development process. Therefore, the total costs to advance any of our product candidates to marketing approval in even a single jurisdiction will be substantial. Because of the numerous risks and uncertainties associated with pharmaceutical product development, we are unable to accurately predict the timing or amount of increased expenses or when, or if, we will be able to begin generating revenue from the commercialization of any products or achieve or maintain profitability. Our expenses will also increase substantially if and as we:

- advance our Phase 2 ACCURACY trial of AL101 for the treatment of recurrent/metastatic adenoid cystic carcinoma, or R/M ACC;
- commence our planned Phase 2/3 RINGSIDE pivotal trial of AL102 for the treatment of desmoid tumors, initiate a Phase 2 clinical trial for relapse refractory T cell acute lymphoma or R/R T-ALL, or obtain and conduct clinical trials for any other product candidates;
- assuming successful completion of our Phase 2 trials of AL101, are required by the FDA to complete Phase 3 clinical trials to support submission of a New Drug Application, or NDA, of AL101;
- develop AL101 or AL102 for other indications and develop other product candidates;
- establish a sales, marketing and distribution infrastructure to commercialize AL101 and/or AL102, if approved, and for any other product candidates for which we may obtain marketing approval;
- maintain, expand and protect our intellectual property portfolio;
- hire additional clinical, scientific and commercial personnel;

- add operational, financial and management information systems and personnel, including personnel to support our product development and planned future commercialization efforts, as well as to support our transition to a public reporting company; and

- acquire or in-license other product candidates or technologies.

Furthermore, our ability to successfully develop, commercialize and license any product candidates and generate product revenue is subject to substantial additional risks and uncertainties, as described under "—Risks Related to Development, Clinical Testing, Manufacturing and Regulatory Approval" and "—Risks Related to Commercialization." As a result, we expect to continue to incur net losses and negative cash flows for the foreseeable future. These net losses and negative cash flows have had, and will continue to have, an adverse effect on our stockholders' equity and working capital. The amount of our future net losses will depend, in part, on the rate of future growth of our expenses and our ability to generate revenues. If we are unable to develop and commercialize one or more product candidates, either alone or through collaborations, or if revenues from any product that receives marketing approval are insufficient, we will not achieve profitability. Even if we do achieve profitability, we may not be able to sustain profitability or meet outside expectations for our profitability. If we are unable to achieve or sustain profitability or to meet outside expectations for our profitability, the value of our common stock will be materially and adversely affected.

Our recurring losses from operations raise substantial doubt regarding our ability to continue as a going concern.

We have incurred significant losses since our inception and have never generated revenue or profit, and it is possible we will never generate revenue or profit. As of December 31, 2021, we had cash and cash equivalents and restricted cash totaling $37.3 million. Based on our current operating plans, and without additional funding, we believe we will not have sufficient funds to meet our obligations within the next twelve months from the issuance of our audited consolidated financial statements that are included elsewhere in this Annual Report on Form 10-K. These factors raise substantial doubt about our ability to continue as a going concern. We will need to raise additional capital to fund our future operations and remain as a going concern. There can be no assurance that we will be able to obtain additional funding on acceptable terms, if at all. To the extent that we raise additional capital through future equity offerings, the ownership interest of common stockholders will be diluted, which dilution may be significant. However, we cannot guarantee that we will be able to obtain any or sufficient additional funding or that such funding, if available, will be obtainable on terms satisfactory to us. In the event that we are unable to obtain any or sufficient additional funding, there can be no assurance that we will be able to continue as a going concern, and we will be forced to [delay, reduce or discontinue our product development programs or commercialization efforts].

Substantial doubt about our ability to continue as a going concern may materially and adversely affect the price per share of our common stock, and it may be more difficult for us to obtain financing. If potential collaborators decline to do business with us or potential investors decline to participate in any future financings due to such concerns, our ability to increase our cash position may be limited. The perception that we may not be able to continue as a going concern may cause others to choose not to deal with us due to concerns about our ability to meet our contractual obligations.

We have prepared our consolidated financial statements on a going concern basis, which contemplates the realization of assets and the satisfaction of liabilities and commitments in the normal course of business. Our audited consolidated financial statements included in this Annual Report on Form 10-K do not include any adjustments to reflect the possible inability of the Company to continue as a going concern within one year after the issuance of such financial statements. If we are unable to continue as a going concern, you could lose all or part of your investment in our Company.

We will require additional capital to fund our operations, and if we fail to obtain necessary financing, we may not be able to complete the development and commercialization of AL101 and AL102.

We expect to spend substantial amounts of capital to complete the development of, seek regulatory approvals for and, if approved, commercialize AL101 and AL102. These expenditures will include costs related to our clinical development and costs associated with our license agreement with Bristol-Myers Squibb Company, or BMS, under which we are obligated to make milestone payments, royalty payments in connection with the sale of resulting products and payments consisting of a portion of all consideration we receive in connection with the sublicense or assignment of any patent rights we licensed from BMS. For more information regarding this agreement, please see "Business—License Agreements."

We anticipate that we will use our cash and cash equivalents, including the net proceeds from our initial public offering, or IPO and other issuances of common stock and short-term restricted bank deposits, to advance the clinical development of AL101 and AL102 and the remainder, if any, for working capital and general corporate purposes.

We will require additional capital to enable us to complete the development and commercialization of AL101 for the treatment of R/M ACC, and R/R T-ALL, AL102 for the treatment of desmoid tumors and any other potential indications, if approved, which we may obtain through equity offerings, debt financings, marketing and distribution arrangements and other collaborations, strategic alliances and licensing arrangements or other sources. Adequate additional financing may not be available to us on acceptable terms, or at all. Our failure to raise capital as and when needed would have a negative effect on our financial condition and our ability to pursue our business strategy. In addition, attempting to secure additional financing may divert the time and attention of our management from day-to-day activities and harm our development efforts.

As noted above, we have identified conditions and events that raise substantial doubt about our ability to continue as a going concern. Because the length of time and activities associated with successful development of AL101 and AL102 is highly uncertain, we are unable to estimate the actual funds we will require for development and any approved marketing and commercialization activities. Our future funding requirements, both near and long-term, will depend on many factors, including, but not limited to:

- the progress, timing, costs and results of our clinical trials of AL101 and AL102 and the development of any future product candidates, including any unforeseen costs we may incur as a result of clinical trial delays due to the COVID-19 pandemic or other causes;
- 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 and timing of completion of commercial-scale manufacturing activities;
- the cost of testing drug substances and drug products at release and during stability programs;
- the cost of defending potential intellectual property disputes, including patent infringement actions brought by third parties against us;
- the effect of competing technological and market developments;
- the costs of operating as a public company;
- the extent to which we in-license or acquire other product candidates or technologies;

- the cost of establishing sales, marketing and distribution capabilities for AL101 and AL102;
- the timing and amount of milestone, royalty and other payments that we may receive or that we may be required to make under our license agreements;
- our ability to establish and maintain collaborations on favorable terms, if at all;
- the costs associated with potential product liability claims, including the costs associated with obtaining insurance against such claims and with defending against such claims; and
- the initiation, progress and timing of our commercialization of AL101 and AL102, if approved.

If we are unable to raise additional capital in sufficient amounts or on terms acceptable to us, we may have to significantly delay, scale back or discontinue the development or commercialization of AL101 and AL102 or potentially discontinue operations.

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

Until such time, if ever, as we can generate sufficient revenue to support our operations, we may finance our cash needs through a combination of equity offerings, debt financings, marketing and distribution arrangements and other collaborations, strategic alliances and licensing arrangements or other sources. We do not currently have any committed external source of funds. In addition, we may seek additional capital due to favorable market conditions or strategic considerations, even if we believe that we have sufficient funds for our current or future operating plans.

To the extent that we raise additional capital through the sale of equity or convertible debt securities, your ownership interest will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect your rights as a common stockholder. Debt financing and preferred equity financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends. If we raise additional funds through marketing and distribution arrangements and other collaborations, strategic alliances and licensing arrangements with third parties, we may be required to relinquish valuable rights to our technologies, intellectual property, future revenue streams or product candidates or grant licenses on terms that may not be favorable to us. If we are unable to raise additional funds through equity or debt financings when needed, we may be required to delay, limit, reduce or terminate product candidate development or future commercialization efforts.

We have a limited operating history and no history of commercializing pharmaceutical products, which may make it difficult to evaluate the prospects for our future viability.

We were established and began operations in November 2017. Our operations to date have been limited to financing and staffing our company, licensing product candidates, developing AL101 for the treatment of R/M ACC, and developing AL102 for the treatment of desmoid tumors and R/R T-ALL, and conducting preclinical studies and clinical trials of AL101 and AL102. We have not yet demonstrated the ability to successfully complete a large-scale, pivotal clinical trial, obtain marketing approval, manufacture a commercial scale product, or arrange for a third party to do so on our behalf, or conduct sales and marketing activities necessary for successful product commercialization. Consequently, predictions about our future success or viability may not be as accurate as they could be if we had a longer operating history or a history of successfully developing and commercializing pharmaceutical products.

In addition, as a business with a limited operating history, we may encounter unforeseen expenses, difficulties, complications, delays and other known and unknown factors. We will eventually need to transition 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 and, as a result, our business may be adversely affected.

As we continue to build our business, we expect our financial condition and operating results may fluctuate significantly from quarter to quarter and year to year due to a variety of factors, many of which are beyond our control. Accordingly, you should not rely upon the results of any particular quarterly or annual period as indications of future operating performance.

We are heavily dependent on the success of AL101 and AL102, our most advanced product candidates, which are still under clinical development, and if either AL101 or AL102 does not receive regulatory approval or is not successfully commercialized, our business may be harmed.

To date, we have invested a significant portion of our efforts and financial resources in the development of AL101 for the treatment of R/M ACC, and in the development of AL102 for the treatment of desmoid tumors, R/R T-ALL and MM. Our future success is substantially dependent on our ability to successfully complete clinical development for, obtain regulatory approval for and successfully commercialize AL101 and AL102, which may never occur. We currently have no products that are approved for commercial sale and may never be able to develop a marketable product. We expect that a substantial portion of our efforts and expenditures over the next few years will be devoted to AL101 and AL102, which will require additional clinical development, management of clinical and manufacturing activities, regulatory approval in multiple jurisdictions, obtaining manufacturing supply, building of a commercial organization, substantial investment and significant marketing efforts before we can generate any revenues from any commercial sales. We cannot be certain that we will be able to successfully complete any of these activities.

The research, testing, manufacturing, labeling, approval, sale, marketing and distribution of drug products are subject to extensive regulation by the FDA and comparable foreign regulatory authorities. We are not permitted to market AL101 and AL102 in the United States until we receive approval of an NDA from the FDA, or in any foreign countries until we receive the requisite approval from such countries. We have not submitted an NDA to the FDA or comparable applications to other regulatory authorities for AL101 and AL102 and may not be in a position to do so for several years, if ever. If we are unable to obtain the necessary regulatory approvals for AL101 or AL102, we will not be able to commercialize AL101 and AL102 and our financial position will be materially adversely affected and we may not be able to generate sufficient revenue to continue our business.

We may be required to make significant payments under our license of AL101 and AL102 from BMS.

In November 2017, we licensed rights to AL101 and AL102 pursuant to a license agreement with BMS, or the BMS License Agreement. Under the BMS License Agreement, we are subject to significant obligations, including milestone payments, royalty payments on product sales and clinical development obligations, as well as other material obligations. Under the BMS License Agreement, we will be obligated to pay BMS fixed royalty payments that could range from a high single-digit to a low teen percentage on net sales of products containing AL101 or AL102, as well as a portion of all consideration we receive in connection with the sublicense or assignment of any patent rights we licensed from BMS, ranging from a mid-teen to mid-double-digit percentage, depending on the development stage of the most advanced product candidate that is subject to the applicable sublicense or assignment. For more information regarding the BMS License Agreement, please see "Business—License Agreements." If these payments become due under the terms of the BMS License Agreement, we may not have sufficient funds available to meet our obligations and our development efforts may be materially harmed. Furthermore, if we are forced to raise additional funds, we may be required to delay, limit, reduce or terminate our product development or future commercialization efforts, or grant rights to develop and market product candidates that we would otherwise develop and market ourselves.

Due to our limited resources and access to capital, we must prioritize development of certain programs and product candidates; these decisions may prove to be wrong and may adversely affect our business.

We may fail to identify and acquire, through purchase or license, viable new product candidates for clinical development for a number of reasons. If we fail to identify and acquire additional product candidates, our business could be materially harmed.

Efforts to identify and pursue new product candidates and disease targets require substantial technical, financial and human resources, regardless of whether they are ultimately successful. Programs may initially show promise in preclinical studies, yet fail to yield positive results during clinical development for a number of reasons, including:

- the methodology used may not be successful in identifying potential indications and/or product candidates; or
- product candidates may, after further study, be shown to have harmful adverse effects or other characteristics that indicate they are unlikely to be effective products.

Because we have limited financial and human resources, we intend to initially focus on programs and product candidates for a limited set of indications. As a result, we may forego or delay pursuit of opportunities with other product candidates or for other indications with our existing product candidates that may later prove to have greater commercial potential or a greater likelihood of success. We may focus our efforts and resources on potential product candidates or other potential programs that ultimately prove to be unsuccessful.

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

As of December 31, 2021, we had 35 employees. We expect to experience significant growth in the number of our employees and the scope of our operations, particularly in the areas of product candidate development, regulatory affairs and sales and marketing. We may have difficulty identifying, hiring and integrating new personnel. Future growth would impose significant additional responsibilities on our management, including the need to identify, recruit, maintain, motivate and integrate additional employees, consultants and contractors. Also, our management may need to divert a disproportionate amount of its attention away from our day-to-day activities and devote a substantial amount of time to managing these growth activities. We may not be able to effectively manage the expansion of our operations, which may result in weaknesses in our infrastructure, give rise to operational mistakes, loss of business opportunities, loss of employees and reduced productivity among remaining employees. Our expected growth could require significant capital expenditures and may divert financial resources from other projects, such as the development of product candidates. If our management is unable to effectively manage our growth, our expenses may increase more than expected, our ability to generate and/or grow revenues could be reduced, and we may not be able to implement our business strategy. Our future financial performance and our ability to commercialize our product candidates and compete effectively will depend, in part, on our ability to effectively manage any future growth.

Many of the biotechnology companies that we compete against for qualified personnel and consultants have greater financial and other resources, different risk profiles and a longer history in the industry than we do. If we are unable to continue to attract and retain high-quality personnel and consultants, the rate and success at which we can discover and develop product candidates and operate our business will be limited.

COVID-19 may adversely affect our business, including our clinical trials.

The COVID-19 pandemic and government measures taken in response have had significant direct and indirect impacts on businesses and commerce, as worker shortages have occurred, supply chains have been disrupted, facilities and production have been suspended, and demand for certain goods and services, such as medical services and supplies, has spiked, while demand for other goods and services, such as travel, has fallen. In response to the spread of COVID-19, our administrative employees work remotely at times. In addition, we have modified our business practices, including restricting a portion of employee travel, developing social distancing plans for some of our employees and canceling some physical participation in meetings, events and conferences. As a result of the COVID-19 pandemic, we may experience additional disruptions that could severely impact our business, preclinical studies and clinical trials, including:

- delays or difficulties in enrolling patients in our clinical trials;
- delays or difficulties in clinical site initiation, including difficulties in recruiting clinical site investigators and clinical site staff;
- diversion of healthcare resources away from the conduct of clinical trials, including the diversion of hospitals serving as our clinical trial sites and hospital staff supporting the conduct of our clinical trials;
- interruption of key clinical trial activities, such as clinical trial site data monitoring, due to limitations on travel imposed or recommended by federal or state governments, employers and others or interruption of clinical trial subject visits and study procedures (such as endoscopies that are deemed non-essential), which may impact the integrity of subject data and clinical study endpoints;
- interruption or delays in the operations of the FDA or other regulatory authorities, which may impact review and approval timelines;
- interruption of, or delays in receiving, supplies of our product candidates from our contract manufacturing organizations due to staffing shortages, production slowdowns or stoppages and disruptions in delivery systems;
- limitations on employee resources that would otherwise be focused on the conduct of our clinical trials, including because of sickness of employees or their families or the desire of employees to avoid contact with large groups of people; and
- interruption or delays to our sourced discovery and clinical activities.

In addition, the outbreak and the resulting government actions may adversely impact our planned and ongoing clinical trials. Clinical site initiation, including difficulties in recruiting clinical site investigators and clinical site staff, and patient enrollment may be delayed due to prioritization of hospital resources toward the COVID-19 pandemic. Some patients may not be willing and/or able to comply with clinical trial protocols due to the COVID-19 pandemic, particularly if quarantines impede patient movement or interrupt healthcare services. Similarly, our ability to recruit and retain patients and principal investigators and site staff who, as healthcare providers, may have heightened exposure to COVID-19 may be impeded, which would adversely impact our clinical trial operations. The diversion of healthcare resources away from the conduct of clinical trials to focus on pandemic concerns, including the attention of physicians serving as our clinical trial investigators and hospitals serving as our clinical trial sites, diversion of hospitals and medical centers or sites serving as our clinical trial sites and hospital or other staff supporting the conduct of our clinical trials may significantly disrupt our research activities. As a result, the expected timeline for data readouts of our clinical trials and certain regulatory filings will likely be negatively impacted, which would adversely affect and delay our ability to obtain regulatory approvals for our product candidates, increase our operating expenses and have a material adverse effect on our financial condition.

Furthermore, the response to the COVID-19 pandemic may redirect resources with respect to regulatory matters and intellectual property matters in a way that would adversely impact our ability to progress regulatory approvals and protect our intellectual property. In addition, we may face impediments to regulatory meetings and approvals due to measures intended to limit in-person interactions. For example, in response to the COVID-19 pandemic, in March 2020, the FDA announced its intention to postpone most inspections of foreign manufacturing facilities, and on March 18, 2020, the FDA temporarily postponed routine surveillance inspections of domestic manufacturing facilities. Subsequently, in July 2020, the FDA resumed certain on-site inspections of domestic manufacturing facilities subject to a risk-based prioritization system. The FDA utilized this risk-based assessment system to assist in determining when and where it was safest to conduct prioritized domestic inspections. Additionally, on April 15, 2021, the FDA issued a guidance document in which the FDA described its plans to conduct voluntary remote interactive evaluations of certain drug manufacturing facilities and clinical research sites, among other facilities. According to the guidance, the FDA may request such remote interactive evaluations where the FDA determines that remote evaluation would be appropriate based on mission needs and travel limitations. In May 2021, the FDA outlined a detailed plan to move toward a more consistent state of inspectional operations, and in July 2021, the FDA resumed standard inspectional operations of domestic facilities and was continuing to maintain this level of operation as of September 2021. More recently, the FDA has continued to monitor and implement changes to its inspectional activities to ensure the safety of its employees and those of the firms it regulates as it adapts to the evolving COVID-19 pandemic. Regulatory authorities outside the United States have adopted similar restrictions or other policy measures in response to the COVID-19 pandemic. If a prolonged government shutdown occurs, or if global health concerns continue to hinder or prevent the FDA or other regulatory authorities from conducting their regular inspections, reviews or other regulatory activities, it could significantly impact the ability of the FDAor other regulatory authorities to timely review and process our regulatory submissions, which could have a material adverse effect on our business.

The COVID-19 pandemic continues to rapidly evolve. The extent to which the outbreak impacts our business, preclinical studies and clinical trials will depend on future developments, which are highly uncertain and cannot be predicted with confidence, such as the ultimate geographic spread, trajectory, and duration of the pandemic, including due to the emergence of variants; travel restrictions in the United States Canada, Europe, Israel and other regions; business closures or business disruptions; the effectiveness of vaccines, vaccine distribution efforts, and other treatments; and the effectiveness of other actions taken in the United States, Canada, Europe, Israel and other regions to contain the pandemic. As a result, the COVID-19 pandemic could have a material adverse effect on our business, results of operations, financial condition and prospects and heighten many of our known risks described in this “Risk Factors” section.

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

As of December 31, 2021, we had net operating loss carryforwards, or NOLs, of $91.6 million for federal income tax purposes and $57.7 million for state income tax purposes, which may be available to offset our future taxable income, if any, and begin to expire in various amounts in 2037 and 2038, respectively, provided that NOLs generated in tax years ending after December 31, 2017 will not be subject to expiration. In general, under Sections 382 and 383 of the U.S. 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 use its pre-change NOLs and certain other tax attributes to offset future taxable income. If the U.S. Internal Revenue Service challenges our determinations with respect to the existence of previous ownership changes or the effects thereof, our ability to use our NOLs could be limited by Section 382 of the Code. Future changes in our stock ownership, some of which are outside of our control, could also result in an ownership change under Sections 382 and 383 of the Code. In addition, for taxable years beginning after December 31, 2020, utilization of federal NOLs generated in tax years beginning after December 31, 2017 are limited to a maximum of 80% of the taxable income for such year, after taking into account utilization of NOLs generated in years beginning before January 1, 2018 and determined without regard to such NOL deduction. Furthermore, our ability to use NOLs of companies that we may acquire in the future may be subject to limitations. For these reasons, we may not be able to use a material portion of the NOLs, even if we attain profitability.

Risks Related to Development, Clinical Testing, Manufacturing and Regulatory Approval

Our product candidates are designed for patients with genetically defined cancers, which is a rapidly evolving area of science, and the approach we are taking to discover and develop product candidates is novel and may never lead to marketable products.

The discovery and development of targeted therapies for patients with genetically defined cancers is an emerging field, and the scientific discoveries that form the basis for our efforts to discover and develop product candidates are relatively new. The scientific evidence to support the feasibility of developing product candidates based on these discoveries is both preliminary and limited. The patient populations for our product candidates are not completely defined but are substantially smaller than the general treated cancer population, and we will need to screen and identify these patients. Successful identification of patients is dependent on several factors, including achieving certainty as to how specific genetic alterations respond to our product candidates and developing companion diagnostics to identify such genetic alterations. Furthermore, even if we are successful in identifying patients, we cannot be certain that the resulting patient populations will be large enough to allow us to successfully conduct clinical trials, and if approved, commercialize our products and achieve profitability. Therefore, we do not know if our approach of treating patients with genetically defined cancers will be successful, and if our approach is unsuccessful, our business will suffer.

Clinical trials are expensive, time-consuming and difficult to design and implement, and involve an uncertain outcome.

Before obtaining marketing approval from the FDA or other comparable foreign regulatory authorities for the sale of our product candidates, we must complete preclinical development and extensive clinical trials to demonstrate the safety and efficacy of our product candidates. Clinical testing is expensive and can take many years to complete, and its outcome is inherently uncertain. Failure can occur at any time during the clinical trial process. We may experience delays in initiating and completing any clinical trials that we are conducting or intend to conduct, including as a result of the COVID-19 pandemic, and we do not know whether our ongoing or planned clinical trials will begin or progress on schedule, need to be redesigned, enroll patients on time or be completed on schedule, or at all. Clinical trials can be delayed for a variety of reasons, including delays related to:

- the FDA or comparable foreign regulatory authorities disagreeing as to the design or implementation of our clinical studies;
- obtaining regulatory authorizations to commence a trial or consensus with regulatory authorities on trials design;
- reaching an agreement on acceptable terms with prospective contract research organizations, or CROs, and clinical trial sites, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and trial sites;
- obtaining Institutional Review Board, or IRB, approval at each site, or Independent Ethics Committee, or IEC, approval at sites outside the United States;
- changes to clinical trial protocols;
- recruiting suitable patients to participate in a trial in a timely manner and in sufficient numbers;
- having patients complete a trial or return for post-treatment follow-up;
- imposition of a clinical hold by regulatory authorities, including as a result of unforeseen safety issues or side effects or failure of trial sites to adhere to regulatory requirements or follow trial protocols;
- clinical sites deviating from trial protocol or dropping out of a trial;
- addressing patient safety concerns that arise during the course of a trial;
- the occurrence of serious adverse events in trials of the same class of agents conducted by other companies;
- subjects choosing an alternative treatment for the indication for which we are developing our product candidates, or participating in competing clinical trials;
- adding a sufficient number of clinical trial sites;
- manufacturing sufficient quantities of product candidate with sufficient quality for use in clinical trials;
- lack of adequate funding to continue the clinical trial;

- selection of clinical end points that require prolonged periods of clinical observation or analysis of the resulting data;
- a facility manufacturing our product candidates or any of their components being ordered by the FDA or comparable foreign regulatory authorities to temporarily or permanently shut down due to violations of current good manufacturing practice, or cGMP, regulations or other applicable requirements, or infections or cross-contaminations of product candidates in the manufacturing process;
- any changes to our manufacturing process that may be necessary or desired;
- third-party clinical investigators losing the licenses or permits necessary to perform our clinical trials, not performing our clinical trials on our anticipated schedule or consistent with the clinical trial protocol, good clinical practices, or GCP, or other regulatory requirements;
- third-party contractors not performing data collection or analysis in a timely or accurate manner; or
- third-party contractors becoming debarred or suspended or otherwise penalized by the FDA or other government or regulatory authorities for violations of regulatory requirements, in which case we may need to find a substitute contractor, and we may not be able to use some or all of the data produced by such contractors in support of our marketing applications.

In addition, disruptions caused by the COVID-19 pandemic may increase the likelihood that we encounter such difficulties or delays in initiating, enrolling, conducting or completing our planned and ongoing clinical trials. We could also encounter delays if a clinical trial is suspended or terminated by us, the IRBs or IECs of the institutions in which such trials are being conducted, the Data Safety Monitoring Board, or DSMB, for such trial or the FDA or other regulatory authorities. Such authorities may impose such a suspension or termination due to a number of factors, including failure to conduct the clinical trial in accordance with regulatory requirements or our clinical protocols, inspection of the clinical trial operations or trial site by the FDA or other regulatory authorities resulting in the imposition of a clinical hold, unforeseen safety issues or adverse side effects, failure to demonstrate a benefit from using a drug, changes in governmental regulations or administrative actions or lack of adequate funding to continue the clinical trial. Furthermore, we rely on CROs and clinical trial sites to ensure the proper and timely conduct of our clinical trials and, while we have agreements governing their committed activities, we have limited influence over their actual performance, as described in "—Risks Related to Our Dependence on Third Parties."

We have limited experience in designing clinical trials and may be unable to design and execute a clinical trial which, if successful, would represent a well-controlled trial for purposes of seeking marketing approval. It may be necessary to re-design our clinical trials, including to conduct clinical trials of our product candidates in combination with other therapies, in an effort to achieve the response rates sufficient to support marketing approval. We cannot be certain that our ongoing or planned clinical trials or any other future clinical trials will be successful. Additionally, any safety concerns observed in any one of our clinical trials in our targeted indications could limit the prospects for regulatory approval of our product candidates in those and other indications, which could seriously harm our business.

Further, conducting clinical trials in foreign countries, as we may do for our product candidates, presents additional risks that may delay completion of our clinical trials. These risks include the failure of enrolled patients in foreign countries to adhere to clinical protocol as a result of differences in healthcare services or cultural customs, managing additional administrative burdens associated with foreign regulatory schemes, as well as political and economic risks relevant to such foreign countries.

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

If we experience delays in the commencement or completion of any clinical trials, or if we terminate a clinical trial prior to completion, the commercial prospects of AL101, AL102 or any other product candidate we develop could be harmed, and our ability to generate revenues may be delayed. In addition, any delays in our clinical trials could increase our costs, slow the development and approval process and jeopardize our ability to commence product sales and generate revenues. Any of these occurrences may harm our business, financial condition and results of operations. In addition, many of the factors that cause, or lead to, a delay in the commencement or completion of clinical trials may also ultimately lead to the denial of regulatory approval of our product candidates.

In addition, the FDA's and other regulatory authorities' policies with respect to clinical trials may change and additional government regulations may be enacted. For instance, the regulatory landscape related to clinical trials in the EU recently evolved. The EU Clinical Trials Regulation, or CTR, which was adopted in April 2014 and repeals the EU Clinical Trials Directive, became applicable on January 31, 2022. While the Clinical Trials Directive required a separate clinical trial application, or CTA, to be submitted in each member state, to both the competent national health authority and an independent ethics committee, the CTR introduces a centralized process and only requires the submission of a single application to all member states concerned. The CTR allows sponsors to make a single submission to both the competent authority and an ethics committee in each member state, leading to a single decision per member state. The assessment procedure of the CTA has been harmonized as well, including a joint assessment by all member states concerned, and a separate assessment by each member state with respect to specific requirements related to its own territory, including ethics rules. Each member state's decision is communicated to the sponsor via the centralized EU portal. Once the CTA is approved, clinical study development may proceed. The CTR foresees a three-year transition period. The extent to which ongoing and new clinical trials will be governed by the CTR varies. For clinical trials whose CTA was made under the Clinical Trials Directive before January 31, 2022, the Clinical Trials Directive will continue to apply on a transitional basis for three years. Additionally, sponsors may still choose to submit a CTA under either the Clinical Trials Directive or the CTR until January 31, 2023 and, if authorized, those will be governed by the Clinical Trials Directive until January 31, 2025. By that date, all ongoing trials will become subject to the provisions of the CTR. Compliance with the CTR requirements by us and our third-party service providers, such as CROs, may impact our developments plans

It is currently unclear to what extent the UK will seek to align its regulations with the EU. The UK regulatory framework in relation to clinical trials is derived from existing EU legislation (as implemented into UK law, through secondary legislation). On January 17, 2022, the UK Medicines and Healthcare products Regulatory Agency, or MHRA, launched an eight-week consultation on reframing the UK legislation for clinical trials. The consultation closed on March 14, 2022 and aims to streamline clinical trials approvals, enable innovation, enhance clinical trials transparency, enable greater risk proportionality, and promote patient and public involvement in clinical trials. The outcome of the consultation will be closely watched and will determine whether the UK chooses to align with the regulation or diverge from it to maintain regulatory flexibility. A decision by the UK not to closely align its regulations with the new approach that will be adopted in the EU may have an effect on the cost of conducting clinical trials in the UK as opposed to other countries and/or make it harder to seek a marketing authorization in the EU for our product candidates on the basis of clinical trials conducted in the UK.

If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies governing clinical trials, our development plans may be impacted.

We were not involved in the early development of our lead product candidates; therefore, we are dependent on third parties having accurately generated, collected and interpreted data from certain preclinical studies and clinical trials for our product candidates.

We licensed exclusive worldwide rights to AL101 and AL102 from BMS in November 2017, and were not involved in or able to control the development of AL101 and AL102 prior to such time. While BMS is contractually obligated to provide all data it generated from preclinical studies and clinical trials conducted for AL101 and AL102 prior to our licensing of such products, in certain instances we are currently reliant upon reports BMS generated analyzing such data. In the event further data is required by a regulatory authority or otherwise in our development of AL101 and/or AL102 and BMS does not comply with its contractual obligation to provide such data, we could incur increased costs in re-analyzing certain preclinical and clinical data and will experience delays in the development of AL101 and AL102, which could adversely affect our financial position and delay our ability to commercialize AL101 and AL102.

The regulatory approval processes of the FDA and comparable foreign authorities are lengthy, time consuming and inherently unpredictable, and if we are ultimately unable to obtain regulatory approval for AL101, AL102 or any other product candidates, our business will be substantially harmed.

The time required to obtain approval by the FDA and comparable foreign authorities is unpredictable but 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, which may cause delays in the approval or the decision not to approve an application. Regulatory authorities have substantial discretion in the approval process and may refuse to accept any application or may decide that our data are insufficient for approval and require additional preclinical, clinical or other data. Even if we eventually complete clinical testing and receive approval of any regulatory filing for our product candidates, the FDA and other comparable foreign regulatory authorities may approve our product candidates for a more limited indication or a narrower patient population than we originally requested. We have not obtained regulatory approval for any product candidate and it is possible that we will never obtain regulatory approval for AL101, AL102 or any other product candidate. We are not permitted to market any of our product candidates in the United States until we receive regulatory approval of an NDA from the FDA, or in any foreign countries until we receive the requisite approval from foreign regulatory authorities.

Prior to obtaining approval to commercialize a 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 foreign regulatory agencies, that such product candidate is safe and effective for its intended use. Results from preclinical studies and clinical trials can be interpreted in different ways. Even if we believe the preclinical or clinical data for our product candidates are promising, such data may not be sufficient to support approval by the FDA and other regulatory authorities.

The FDA or any foreign regulatory bodies can delay, limit or deny approval of our product candidates or require us to conduct additional preclinical or clinical testing or abandon a program for many reasons, including:

- the FDA or comparable foreign regulatory authorities may disagree with the design or implementation of our clinical trials;
- we may be unable to demonstrate to the satisfaction of the FDA or comparable foreign regulatory authorities that a product candidate is safe and effective for its proposed indication;
- serious and unexpected drug-related side effects experienced by participants in our clinical trials or by individuals using drugs similar to our product candidates, or other products containing the active ingredient in our product candidates;
- negative or ambiguous results from our clinical trials or results that may not meet the level of statistical significance required by the FDA or comparable foreign regulatory authorities for approval;
- the population studied in the clinical trial may not be sufficiently broad or representative to assure efficacy and safety in the full population for which we seek approval;
- we may be unable to demonstrate that a product candidate's clinical and other benefits outweigh its safety risks;
- the FDA or comparable foreign regulatory authorities may disagree with our interpretation of data from preclinical studies or clinical trials;
- the data collected from clinical trials of our product candidates may not be acceptable or sufficient to support the submission of an NDA or other submission or to obtain regulatory approval in the United States or elsewhere, and we may be required to conduct additional clinical trials;
- the FDA's or the applicable foreign regulatory agency's disagreement regarding the formulation, labeling and/or the specifications of our product candidates;
- the FDA or comparable foreign regulatory authorities may fail to approve or find deficiencies with the manufacturing processes or facilities of third-party manufacturers with which we contract for clinical and commercial supplies; and
- the approval policies or regulations of the FDA or comparable foreign regulatory authorities may significantly change in a manner rendering our clinical data insufficient for approval.

Moreover, preclinical and clinical data are often susceptible to varying interpretations and analyses and many companies that believed their product candidates performed satisfactorily in preclinical studies and clinical trials nonetheless failed to obtain FDA or comparable foreign regulatory authority approval. We cannot guarantee that the FDA or foreign regulatory authorities will interpret trial results as we do, and more trials could be required before we are able to submit applications seeking approval of our product candidates. To the extent that the results of the trials are not satisfactory to the FDA or foreign regulatory authorities for support of a marketing application, we may be required to expend significant resources, which may not be available to us, to conduct additional trials in support of potential approval of our product candidates. Furthermore, the approval policies or regulations of the FDA or comparable foreign regulatory authorities may significantly change in a manner rendering our clinical data insufficient for approval, which may lead to the FDA or comparable foreign regulatory authorities delaying, limiting or denying approval of our product candidates.

Of the large number of drugs in development, only a small percentage successfully complete the regulatory approval processes and are commercialized. This lengthy approval process, as well as the unpredictability of future clinical trial results, may result in our failing to obtain regulatory approval to market AL101, AL102 or any other product candidate, which would significantly harm our business, results of operations and prospects.

In addition, the FDA or the applicable foreign regulatory agency also may approve a product candidate for a more limited indication or patient population than we originally requested, and the FDA or applicable foreign regulatory agency may approve a product candidate with a Risk Evaluation and Mitigation Strategy, or REMS, or similar risk management measures, or a label that does not include the labeling claims necessary or desirable for the successful commercialization of that product candidate. Regulatory authorities may also grant approval contingent on the performance of costly post-marketing clinical trials. Any of the foregoing scenarios could materially harm the commercial prospects for our product candidates.

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

The timely completion of clinical trials in accordance with their protocols depends, among other things, on our ability to enroll a sufficient number of patients who remain in the study until its conclusion. We may encounter delays in enrolling, or be unable to enroll, a sufficient number of patients to complete any of our clinical trials, and 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 and nature of the patient population;
- the severity of the disease under investigation;
- the patient eligibility criteria defined in the protocol;
- the size of the patient population required for analysis of the trial's primary endpoints;
- the nature of the trial protocol;
- the existing body of safety and efficacy data with respect to the product candidate;
- the number of clinical sites and the proximity of patients to clinical sites;
- our ability to recruit clinical trial investigators with the appropriate competencies and experience;
- clinicians' and patients' perceptions as to the potential advantages of the product candidate being studied in relation to other available therapies, including any new drugs that may be approved for the indications we are investigating;
- competing clinical trials being conducted by other companies or institutions;
- the COVID-19 pandemic;
- our ability to maintain patient consents; and
- the risk that patients enrolled in clinical trials will drop out of the trials before completion.

Furthermore, any negative results we may report in clinical trials of any product candidate 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 or program delays, which could have a harmful effect on our strategy to rapidly advance the clinical development of our product candidates or could render further development impossible.

If we do not achieve our projected development and commercialization goals in the timeframes we announce and expect, the commercialization of our product candidates may be delayed and our business will be harmed.

For planning purposes, we sometimes estimate the timing of the accomplishment of various scientific, clinical, regulatory and other product development objectives. These milestones may include our expectations regarding the commencement or completion of scientific studies and clinical trials, the regulatory submissions or commercialization objectives. From time to time, we may publicly announce the expected timing of some of these milestones, such as the completion of an ongoing clinical trial, the initiation of other clinical trials, receipt of regulatory approval or the commercial launch of a product. The achievement of many of these milestones may be outside of our control. All of these milestones are based on a variety of assumptions which may cause the timing of achievement of the milestones to vary considerably from our estimates, including:

- our available capital resources or capital constraints we experience;
- the rate of progress, costs and results of our clinical trials and research and development activities, including the extent of scheduling conflicts with participating clinicians and collaborators;
- our ability to identify and enroll patients who meet clinical trial eligibility criteria;
- our receipt of authorizations by the FDA and comparable foreign regulatory authorities, and the timing thereof;
- other actions, decisions or rules issued by regulators;
- our ability to access sufficient, reliable and affordable supplies of materials used in the manufacture of our product candidates;
- our ability to manufacture and supply clinical trial materials to our clinical sites on a timely basis;
- the severity, duration and impact of the COVID-19 pandemic;
- the efforts of our collaborators with respect to the commercialization of our products, if any; and
- the securing of, costs related to, and timing issues associated with, commercial product manufacturing as well as sales and marketing activities.

If we fail to achieve announced milestones in the timeframes we expect, the commercialization of any of our product candidates may be delayed, and our business, results of operations, financial condition and prospects may be adversely affected.

Results of preclinical studies, early clinical trials or analyses may not be indicative of results obtained in later trials.

The results of preclinical studies, early clinical trials or analyses of our product candidates, including our *post hoc* analyses of AL101 and AL102, may not be predictive of the results of later-stage clinical trials or the results of clinical trials of the same product candidates in other indications. Product candidates in later stages of clinical trials may fail to show the desired safety and efficacy traits despite having progressed through preclinical studies and initial clinical trials. A number of companies in the biopharmaceutical industry have suffered significant setbacks in advanced clinical trials due to lack of efficacy or adverse safety profiles, notwithstanding promising results in earlier trials. In addition, conclusions based on promising data from analyses of clinical results, such as our *post hoc* analyses, may be shown to be incorrect when implemented in prospective clinical trials. Even if our clinical trials of AL101 or AL102 are completed as planned, we cannot be certain that their results will support the safety and efficacy sufficient to obtain regulatory approval. Product candidates in later-stage clinical trials may fail to demonstrate sufficient safety and efficacy to the satisfaction of the FDA and other comparable foreign regulatory authorities despite having progressed through preclinical studies and early-stage clinical trials. Moreover, the results of clinical trials of a product candidate in a particular indication may not be predictive of the results of clinical trials of that product candidate in other indications.

In some instances, there can be significant variability in safety and efficacy results between different clinical trials of the same product candidate due to numerous factors, including changes in trial protocols, differences in size and type of the patient populations, differences in and adherence to the dosing regimen and other trial protocols and the rate of dropout among clinical trial participants. Patients treated with our product candidates may also be undergoing surgical, radiation and chemotherapy treatments and may be using other approved products or investigational new drugs, which can cause side effects or adverse events that are unrelated to our product candidate. As a result, assessments of efficacy and safety can vary widely for a particular patient, and from patient to patient and site to site within a clinical trial. This subjectivity can increase the uncertainty of, and adversely impact, our clinical trial outcomes. We do not know whether any clinical trials we may conduct will demonstrate consistent or adequate efficacy and safety sufficient to obtain marketing approval to market our product candidates. Most product candidates that begin clinical trials are never approved by regulatory authorities for commercialization.

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

From time to time, we may also disclose interim data from our preclinical studies and 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. Adverse differences between interim, top-line or preliminary data and final data could significantly harm our business prospects. Further, disclosure of interim data by us or by our competitors could result in volatility in the price of our common stock.

Further, others, including regulatory agencies, may not accept or agree with our assumptions, estimates, calculations, conclusions or analyses or may interpret or weigh the importance of data differently, which could impact the value of the particular program, the approvability or commercialization of the particular product candidate or product and our company in general. In addition, the information we choose to publicly disclose regarding a particular study or clinical trial is based on what is typically extensive information, and you or others may not agree with what we determine is material or otherwise appropriate information to include in our disclosure.

If the interim top-line or preliminary data that we report differ from actual results, or if others, including regulatory authorities, disagree with the conclusions reached, our ability to obtain approval for, and commercialize, our product candidates may be harmed, which could harm our business, operating results, prospects or financial condition.

Our product candidates may cause serious adverse events or undesirable side effects, which may delay or prevent marketing approval, or, if approved, require them to be taken off the market, require them to include safety warnings or otherwise limit their sales.

As is the case with pharmaceuticals generally, it is likely that there may be side effects and adverse events associated with our product candidates' use. Results of any clinical trial we conduct could reveal a high and unacceptable severity and prevalence of side effects or unexpected characteristics. Serious adverse events or undesirable side effects caused by AL101, AL102 or any other product candidates could cause us or regulatory authorities to interrupt, delay or halt clinical trials and could result in a more restrictive label or the delay or denial of regulatory approval by the FDA or other comparable foreign authorities. Drug-related side effects could affect patient recruitment or the ability of enrolled patients to complete the trial or result in potential product liability claims. Any of these occurrences may harm our business, financial condition and prospects significantly. Patients in our ongoing and planned clinical trials may in the future suffer other serious adverse events or other side effects not observed in our preclinical studies or previous clinical trials. In addition, if our product candidates are used in combination with other therapies, our product candidates may exacerbate adverse events associated with the therapy and the severity and frequency of adverse events may be greater than the cumulative severity and frequency of such adverse events when the therapies are used as monotherapies. Patients treated with our product candidates may also be undergoing surgical, radiation and chemotherapy treatments, which can cause side effects or adverse events that are unrelated to our product candidates, but may still impact the success of our clinical trials. The inclusion of critically ill patients in our clinical trials may result in deaths or other adverse medical events due to other therapies or medications that such patients may be using or due to the gravity of such patients' illnesses.

If unacceptable side effects arise in the development of our product candidates, we, the FDA or comparable foreign regulatory authorities, or the IRBs at the institutions in which our studies are conducted, or the DSMB, if constituted for our clinical trials, could recommend a suspension or termination of our clinical trials, or the FDA or comparable foreign regulatory authorities could order us to cease further development of or deny approval of a product candidate for any or all targeted indications. In addition, drug-related side effects could affect patient recruitment or the ability of enrolled patients to complete a trial or result in potential product liability claims. In addition, these side effects may not be appropriately recognized or managed by the treating medical staff. We expect to have to train medical personnel using our product candidates to understand the side effect profiles for our clinical trials and upon any commercialization of any of our product candidates. Inadequate training in recognizing or managing the potential side effects of our product candidates could result in patient injury or death. Any of these occurrences may harm our business, financial condition and prospects significantly.

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

- regulatory authorities may withdraw approvals of such product;
- regulatory authorities may require additional warnings on the label, such as a "black box" warning or contraindication;

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

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

The market opportunities for AL101 and AL102, if approved, may be smaller than we anticipate.

We expect to initially seek approval of AL101 for the treatment of R/M ACC. Our projections of the number of ACC patients, the number of R/M ACC patients and the proportion of R/M ACC patients with Notch-activating mutations are based on our beliefs and estimates. These estimates have been derived from a variety of sources, including scientific literature, patient foundations and publicly available databases, and may prove to be incorrect. Further, new sources may reveal a change in the estimated number of patients, and the number of patients may turn out to be lower than expected. Additionally, the potential addressable patient population for our current programs or future product candidates may be limited. The ultimate market opportunity for our product candidates will depend on, among other things, the final labeling for such product candidates as agreed with the FDA or comparable foreign regulatory authorities, acceptance by the medical community and patient access, potential competition and drug pricing and reimbursement. Even if we obtain significant market share for any product candidate, if approved, if the potential target populations are small, we may never achieve profitability without obtaining marketing approval for additional indications.

We may not be successful in developing, or collaborating with others to develop, diagnostic tests to identify patients with Notch-activating mutations.

We are currently developing product candidates that target the aberrant activation of the Notch pathway and believe that our product candidates, if approved, would be used as treatments for patients with Notch-activating mutations. Commercially available diagnostic tests are limited in their ability to uncover all potential Notch-activating mutations, as they do not cover all four Notch genes and only uncover simple mutations in the Notch gene locus, such as point mutations, insertions, deletions and copy number variations. These tests are able to detect only a subset of the patients with Notch-activating mutations. To identify additional patients with Notch-activating mutations who we believe may benefit from the use of our product candidates, we intend to collaborate with leading diagnostics companies to improve the testing capabilities for Notch-activating mutations. However, the development of such diagnostic tests is expensive, difficult and we and our collaborators may be unable to successfully do so within a reasonable amount of time with acceptable costs, if at all.

In addition, collaborations are subject to substantial additional risks and uncertainties, as described under "—Risks Related to Our Dependence on Third Parties." For example, if our collaborators do not successfully carry out their contractual duties or obligations or fail to meet expected deadlines, the addressable patient population for our product candidates may be limited. Further, if our relationship with any collaborator terminates, we may not be able to enter into alternative collaborative arrangements or do so on commercially reasonable terms. The occurrence of any of the above will have an adverse impact on our business, financial condition and prospects.

Even if we or our collaborators are successful in developing diagnostic tests that uncover additional Notch-activating mutations, such diagnostic tests may nonetheless fail to gain sufficient market acceptance by physicians, patients, third-party payors and others in the medical community for reasons such as cost, ease of use and belief regarding the effectiveness of our product candidates.

We have never obtained marketing approval for a product candidate and we may be unable to obtain, or may be delayed in obtaining, marketing approval for any of our product candidates.

We have never obtained marketing approval for a product candidate. It is possible that the FDA may refuse to accept for substantive review any NDAs that we submit for our product candidates or may conclude after review of our data that our application is insufficient to obtain marketing approval of our product candidates. If the FDA does not accept or approve our NDAs for our product candidates, it may require that we conduct additional clinical, preclinical or manufacturing validation studies and submit that data before it will reconsider our applications. Depending on the extent of these or any other FDA-required studies, approval of any NDA that we submit may be delayed, or may require us to expend more resources than we have available. It is also possible that additional studies, if performed and completed, may not be considered sufficient by the FDA to approve our NDAs. Similar risks exist in foreign jurisdictions where we would seek marketing authorization for our product candidates.

Any delay in obtaining, or an inability to obtain, marketing approvals would prevent us from commercializing our product candidates, generating revenues and achieving and sustaining profitability. If any of these outcomes occurs, we may be forced to abandon our development efforts for our product candidates, which could significantly harm our business.

Even if we obtain FDA approval for AL101, AL102 or any other product candidate in the United States, we may never obtain approval for or commercialize AL101, AL102 or any other product candidate in any other jurisdiction, which would limit our ability to realize their full market potential.

In order to market any products in any particular jurisdiction, we must establish and comply with numerous and varying regulatory requirements on a country-by-country basis regarding safety and efficacy. Approval by the FDA in the United States does not ensure approval by regulatory authorities in other countries or jurisdictions. However, the failure to obtain approval in one jurisdiction may negatively impact our ability to obtain approval elsewhere. In addition, clinical trials conducted in one country may not be accepted by regulatory authorities in other countries, and regulatory approval in one country does not guarantee regulatory approval in any other country.

Approval processes vary among countries and can involve additional product testing and validation and additional administrative review periods. Seeking foreign regulatory approval could result in difficulties and increased costs for us and require additional preclinical studies or clinical trials which could be costly and time consuming. Regulatory requirements can vary widely from country to country and could delay or prevent the introduction of our products in those countries. We do not have any product candidates approved for sale in any jurisdiction, including in international markets, and we do not have experience in obtaining regulatory approval in international markets. If we fail to comply with regulatory requirements in international markets or to obtain and maintain required approvals, or if regulatory approvals in international markets are delayed, our target market will be reduced and our ability to realize the full market potential of any product we develop will be unrealized.

Additionally, the UK left the EU on January 31, 2020, an event commonly referred to as “Brexit”, under the terms of a withdrawal agreement, entering into a “transition period” which ended on December 31, 2020 during which the UK was essentially treated as a member state of the EU and the regulatory regime remained the same across the UK and the EU. The transition period provided time for the UK and EU to negotiate a framework for partnership for the future, which was then crystallized in the Trade and Cooperation Agreement which became effective on January 1, 2021. Since January 1, 2021, the U.K. operates under a distinct regulatory regime. EU pharmaceutical laws now only apply to the UK in respect of Northern Ireland (as laid out in the Protocol on Ireland and Northern Ireland, including but not limited to marketing authorization applications). Since January 1, 2021, EU laws which have been transposed into U.K. law through secondary legislation continue to be applicable as “retained EU law”.

In addition, following the Brexit vote, the EU moved the European Medicines Agency’s, or the EMA, headquarters from the UK to the Netherlands. This transition may cause disruption in the administrative and medical scientific links between the EMA and the U.K. Medicines and Healthcare products Regulatory Agency, including delays in granting CTA or marketing authorization, disruption of import and export of active substance and other components of new drug formulations, and disruption of the supply chain for clinical trial product and final authorized formulations. The cumulative effects of the disruption to the regulatory framework may add considerably to the development lead time to marketing authorization and commercialization of products in the UK and/or the EU. Any delay in obtaining, or an inability to obtain, any marketing approvals, as a result of Brexit or otherwise, would prevent us from commercializing our product candidates in the UK and/or the EU, and restrict our ability to generate revenue and achieve and sustain profitability. If any of these outcomes occurs, we may be forced to restrict or delay efforts to seek regulatory approval in the UK and/or EU for our product candidates, which could significantly and materially harm our business.

Even if we obtain regulatory approval for AL101, AL102 or any product candidate, we will still face extensive and ongoing regulatory requirements and obligations and any product candidates, if approved, may face future development and regulatory difficulties.

Any product candidate for which we obtain marketing approval, along with the manufacturing processes, post-approval clinical data, labeling, packaging, distribution, adverse event reporting, storage, recordkeeping, export, import, advertising and promotional activities for such product, among other things, will be subject to extensive and ongoing requirements of and review by the FDA and other regulatory authorities. These requirements include submissions of safety and other post-marketing information and reports, establishment registration and drug listing requirements, continued compliance with cGMP and similar foreign requirements relating to manufacturing, quality control, quality assurance and corresponding maintenance of records and documents, requirements regarding the distribution of samples to physicians and recordkeeping and GCP requirements for any clinical trials that we conduct post-approval.

Even if marketing approval of a product candidate is granted, the approval may be subject to limitations on the indicated uses for which the product candidate may be marketed or to the conditions of approval, including a requirement to implement a REMS or similar risk management measures. If any of our product candidates receives marketing approval, the accompanying label may limit the approved indicated use of the product candidate, which could limit sales of the product candidate. The FDA or foreign regulatory authorities may also impose requirements for costly post-marketing studies or clinical trials and surveillance to monitor the safety or efficacy of a product. Violations of the Federal Food, Drug, and Cosmetic Act, or FDCA, relating to the promotion of prescription drugs may lead to FDA enforcement actions and investigations alleging violations of federal and state healthcare fraud and abuse laws, as well as state consumer protection laws. Similar regulations apply in countries outside the United States and may lead to foreign regulatory authorities enforcement actions and investigations.

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

- restrictions on manufacturing such products;
- restrictions on the labeling or marketing of products;
- restrictions on product manufacturing, distribution or use;
- requirements to conduct post-marketing studies or clinical trials;
- warning letters or untitled letters;

- withdrawal of the products from the market;
- refusal to approve pending applications or supplements to approved applications that we submit;
- recall of products;
- fines, restitution or disgorgement of profits or revenues;
- suspension or withdrawal of marketing approvals;
- refusal to permit the import or export of our products;
- product seizure; or
- injunctions or the imposition of civil or criminal penalties.

Further, the FDA's policies may change, and additional government regulations may be enacted that could impose extensive and ongoing regulatory requirements and obligations on any product candidate for which we obtain marketing approval. We also cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative action, either in the United States or abroad. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory compliance, we may be subject to enforcement action and we may not achieve or sustain profitability.

The FDA and other regulatory agencies actively enforce the laws and regulations prohibiting the promotion of drugs for off-label uses.

If any of our product candidates is approved and we are found to have improperly promoted off-label uses of those products, we may become subject to significant liability. The FDA and other regulatory agencies strictly regulate the promotional claims that may be made about prescription products, such as our product candidates, if approved. In particular, a product may not be promoted for uses that are not approved by the FDA or such other regulatory agencies as reflected in the product's approved labeling. If we receive marketing approval for a product candidate, physicians may nevertheless prescribe it to their patients in a manner that is inconsistent with the approved label. If we are found to have promoted such off-label uses, we may become subject to significant liability. The U.S. federal government has levied large civil and criminal fines against companies for alleged improper promotion of off-label use and has enjoined several companies from engaging in off-label promotion. The government has also required that companies enter into consent decrees and/or imposed permanent injunctions under which specified promotional conduct is changed or curtailed. If we cannot successfully manage the promotion of our product candidates, if approved, we could become subject to significant liability, which would materially adversely affect our business and financial condition.

If we are required by the FDA or foreign regulatory authorities to obtain approval or certification of a companion diagnostic device in connection with approval of one of our product candidates, and we do not obtain or face delays in obtaining FDA approval or foreign certification of a companion diagnostic device, we will not be able to commercialize the product candidate and our ability to generate revenue will be materially impaired.

According to FDA guidance, if the FDA determines that a companion diagnostic device is essential to the safe and effective use of a novel therapeutic product or indication, the FDA generally will not approve the therapeutic product or new therapeutic product indication if the companion diagnostic is not also approved or cleared for that indication. We plan to collaborate with patient diagnostic companies during our clinical trial enrollment process to help identify patients with tumor gene alterations that we believe are most likely to respond to our product candidates. If a satisfactory companion diagnostic is not commercially available, we may be required to create or obtain one that would be subject to regulatory approval requirements. The process of obtaining or creating such diagnostic is time consuming and costly.

Companion diagnostics are developed in conjunction with clinical programs for the associated product and are subject to regulation as medical devices by the FDA and comparable foreign regulatory authorities, and, to date, the FDA has required premarket approval of all companion diagnostics for cancer therapies. Generally, when a companion diagnostic is essential to the safe and effective use of a therapeutic product, the FDA requires that the companion diagnostic be approved before or concurrent with approval of the therapeutic product and before a product can be commercialized. The approval of a companion diagnostic as part of the therapeutic product's labeling limits the use of the therapeutic product to only those patients who express the specific genetic alteration that the companion diagnostic was developed to detect.

If the FDA or a comparable foreign regulatory authority requires approval (or certification, or clearance) of a companion diagnostic for any of our product candidates, whether before or after the product candidate obtains marketing approval, we and/or third-party collaborators may encounter difficulties in developing and obtaining approval for these companion diagnostics. Any delay or failure by us or third-party collaborators to develop or obtain regulatory approval of a companion diagnostic could delay or prevent approval or continued marketing of our related product candidates.

We may also experience delays in developing a sustainable, reproducible and scalable manufacturing process for the companion diagnostic or in transferring that process to commercial partners or negotiating insurance reimbursement plans, all of which may prevent us from completing our clinical trials or commercializing our product candidates, if approved, on a timely or profitable basis, if at all.

Inadequate funding for the FDA, the SEC and other government agencies could hinder their ability to hire and retain key leadership and other personnel, prevent new products and services from being developed or commercialized in a timely manner or otherwise prevent those agencies from performing normal business functions on which the operation of our business may rely, which could negatively impact our business.

The ability of the FDA and foreign regulatory authorities to review and approve new products can be affected by a variety of factors, including government budget and funding levels, ability to hire and retain key personnel and accept the payment of user fees, and statutory, regulatory, and policy changes. Average review times at the FDA and foreign regulatory authorities have fluctuated in recent years as a result. In addition, government funding of the Securities and Exchange Commission, or the SEC, and other government agencies on which our operations may rely, including those that fund research and development activities is subject to the political process, which is inherently fluid and unpredictable.

Disruptions at the FDA and other agencies, such as the EMA following its relocation to Amsterdam and resulting staff changes, may also slow the time necessary for new drugs to be reviewed and/or approved by necessary government agencies, which would adversely affect our business. For example, in recent years, including in 2018 and 2019, the U.S. government shut down several times and certain regulatory agencies, such as the FDA and the SEC, had to furlough critical employees and stop critical activities. Separately, in response to the COVID-19 pandemic, the FDA has postponed or limited most of its routine inspectional activities. Regulatory authorities outside the United States have adopted similar restrictions or other policy measures in response to the COVID-19 pandemic. If a prolonged government shutdown occurs, it could significantly impact the ability of the FDA and foreign regulatory authorities to timely review and process our regulatory submissions, which could have a material adverse effect on our business. Further, future government shutdowns could impact our ability to access the public markets and obtain necessary capital in order to properly capitalize and continue our operations.

We have been granted Orphan Drug Designation for AL101 for the treatment of ACC and may seek Orphan Drug Designation for other indications or product candidates, and we may be unable to maintain the benefits associated with Orphan Drug Designation, including the potential for market exclusivity, and may not receive Orphan Drug Designation for other indications or for our other product candidates.

Regulatory authorities in some jurisdictions, including the United States and Europe, may designate drugs intended for relatively small patient populations as orphan drugs. Under the Orphan Drug Act, the FDA may designate a drug as an orphan drug if it is a drug intended to treat a rare disease or condition, which is generally defined as a patient population of fewer than 200,000 individuals in the United States, or a patient population greater than 200,000 in the United States where there is no reasonable expectation that the cost of developing the drug will be recovered from sales in the United States. In the United States, Orphan Drug Designation entitles a party to financial incentives such as opportunities for grant funding toward clinical trial costs, tax advantages and user-fee waivers. In addition, if a product that has Orphan Drug Designation subsequently receives the first FDA approval for the disease for which it has such designation, the product is entitled to orphan drug exclusivity, which means that the FDA may not approve any other applications, including a full NDA to market the same product for the same disease or condition for seven years, except in limited circumstances, such as a showing of clinical superiority to the product with orphan drug exclusivity or where the manufacturer is unable to assure sufficient product quantity. However, Orphan Drug Designation neither shortens the development time or regulatory review time of a drug nor gives the drug any advantage in the regulatory review or approval process.

In May 2019, the FDA granted Orphan Drug Designation to AL101 for the treatment of ACC. We may seek Orphan Drug Designations for AL101 in other indications or for AL102 or other product candidates. There can be no assurances that we will be able to obtain such designations.

Even if we obtain Orphan Drug Designation for any product candidate in specific indications, we may not be the first to obtain marketing approval of such product candidate for the orphan-designated disease or condition due to the uncertainties associated with developing pharmaceutical products. In addition, exclusive marketing rights in the United States may be limited if we seek approval for a disease or condition broader than the orphan-designated indication or may be lost if the FDA later determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantities of the product to meet the needs of patients with the rare disease or condition.

Further, even if we obtain orphan drug exclusivity in the United States for a product, that exclusivity may not effectively protect the product from competition because different drugs with different active moieties can be approved for the same disease or condition. Even after an orphan product is approved, the FDA can subsequently approve the same drug with the same active moiety for the same disease or condition if the FDA concludes that the later drug is safer, more effective or makes a major contribution to patient care. Further, the composition of matter patents for AL101 and AL102 will expire in 2032 and 2033, respectively, and if orphan drug exclusivity does not protect these products from competition, our business and financial condition could be materially adversely affected.

Although we have received fast track designation for AL101, and may seek fast track designation for our other product candidates, such designations may not actually lead to a faster development timeline, regulatory review or approval process.

If a drug is intended for the treatment of a serious condition and nonclinical or clinical data demonstrate the potential to address unmet medical need for this condition, a drug sponsor may apply for fast track designation. The sponsor of a fast track product candidate has opportunities for more frequent interactions with the applicable FDA review team during product development and, once an NDA is submitted, the product candidate may be eligible for priority review. A fast track product candidate may also be eligible for rolling review, where the FDA may consider for review sections of the NDA on a rolling basis before the complete application is submitted, 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. Fast track designation alone does not guarantee qualification for the FDA's priority review procedures.

We have received fast track designation for AL101 for the treatment of patients with R/M ACC, and we may seek fast track designations for additional indications for AL101 or for our other product candidates. However, the FDA has broad discretion whether or not to grant such designations. If we seek a designation for a product candidate, we may not receive it from the FDA. Even if we receive it, such designation does not ensure that we will receive marketing approval or that approval will be granted within any particular time frame. We may not experience a faster development or regulatory review or approval process compared to conventional FDA procedures. In addition, the FDA may withdraw a designation if it believes that the designation is no longer supported by data from our clinical development program.

We may attempt to secure approval from the FDA or comparable foreign regulatory authorities through the use of accelerated approval pathways or comparable pathways in foreign countries. If we are unable to obtain such approval, we may be required to conduct additional preclinical studies or clinical trials beyond those that we contemplate, which could increase the expense of obtaining, and delay the receipt of, necessary marketing approvals. Even if we receive accelerated approval from the FDA, 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 may in the future seek an accelerated approval for one or more of our product candidates. Under the accelerated approval program, the FDA may grant accelerated approval to a product candidate designed to treat a serious or life-threatening condition that provides meaningful therapeutic benefit over available therapies upon a determination that the product candidate has 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, such as irreversible morbidity or mortality. 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 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 usually contingent on the sponsor's agreement to conduct, in a diligent manner, additional post-approval confirmatory studies to verity and describe the drug's clinical benefit. If such post-approval studies fail to confirm the drug's clinical benefit, the FDA may withdraw its approval of the drug on an expedited basis.

Prior to seeking accelerated approval for any of our product candidates, we intend to seek feedback from the FDA and will otherwise evaluate our ability to seek and receive accelerated approval. There can be no assurance that after our evaluation of the feedback and other factors we will decide to pursue or submit an NDA for accelerated approval or any other form of expedited development, review or approval. Similarly, there can be no assurance that after subsequent FDA feedback we will continue to pursue or apply for accelerated approval or any other form of expedited development, review or approval, even if we initially decide to do so. Furthermore, if we decide to submit an application for accelerated approval or receive an expedited regulatory designation for our product candidates, there can be no assurance that such submission or application will be accepted or that any expedited development, review or approval will be granted on a timely basis, or at all. The FDA or other comparable foreign regulatory authorities could also require us to conduct further studies prior to considering our application or granting approval of any type. A failure to obtain accelerated approval or any other form of expedited development, review or approval for our product candidate would result in a longer time period to commercialization of such product candidate, could increase the cost of development of such product candidate and could harm our competitive position in the marketplace.

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

As product candidates proceed through preclinical studies to late-stage clinical trials towards potential approval and commercialization, it is common that various aspects of the development program, such as manufacturing methods and formulation, are altered along the way in an effort to optimize processes and results. Such changes carry the risk that they will not achieve these intended objectives. Any of these changes could cause our product candidates to perform differently and affect the results of planned clinical trials or other future clinical trials conducted with the materials manufactured using altered processes. Such changes may also require additional testing, including bridging or comparability testing to demonstrate the validity of clinical data obtained in clinical trials following manufacturing changes, FDA or foreign regulatory authorities' notification or FDA or foreign regulatory authorities' approval.

Because certain of our prior clinical trials of AL101 and AL102 were conducted by third parties, we will need to perform analytical and other tests to demonstrate that any new drug product material is comparable in all respects, including potency, to the product used in such earlier clinical trials. There is no assurance that any such product will pass the required comparability testing, that any other future third-party manufacturer that we engage will be successful in producing our product candidates or that any materials produced by any third-party manufacturer that we engage will have the same effect in patients that we have observed to date with respect to materials used in prior clinical trials.

All of the above could delay completion of clinical trials, require the conduct of bridging clinical trials or the repetition of one or more clinical trials, increase clinical trial costs, delay approval of our product candidates and jeopardize our ability to commence sales and generate revenue.

Moreover, we have not yet manufactured or processed on a commercial scale and may not be able to do so for any of our product candidates if approved. We may make changes as we work to optimize our manufacturing processes, but we cannot be sure that even minor changes in our processes will result in therapies that are safe and effective and approved for commercial sale.

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

The use of AL101, AL102 or any other product candidates we may develop in clinical trials and the sale of any products for which we obtain marketing approval expose us to the risk of product liability claims. Product liability claims might be brought against us by patients, healthcare providers, pharmaceutical companies or others selling or otherwise coming into contact with our products. On occasion, large judgments have been awarded in class action lawsuits based on drugs that had unanticipated adverse effects. If we cannot successfully defend against product liability claims, we could incur substantial liability and costs. In addition, regardless of merit or eventual outcome, product liability claims may result in:

- impairment of our business reputation and significant negative media attention;
- withdrawal of participants from our clinical trials;

- significant costs to defend the litigation;
- distraction of management's attention from our primary business;
- substantial monetary awards to patients or other claimants;
- inability to commercialize AL101, AL102 or any other product candidate;
- product recalls, withdrawals or labeling, marketing or promotional restrictions;
- decreased market demand for any product, if approved; and
- loss of revenue.

Our insurance policies are expensive and protect us only from some business risks, which leaves us exposed to significant uninsured liabilities.

We currently carry insurance with an aggregate of $10.0 million in coverage. However, we do not carry insurance for all categories of risk that our business may encounter. Some of the policies we currently maintain include general liability, property, umbrella, clinical trials and directors' and officers' insurance.

Any additional product liability insurance coverage we acquire in the future, may not be sufficient to reimburse us for any expenses or losses we may suffer. Moreover, insurance coverage is becoming increasingly expensive and in the future we may not be able to maintain insurance coverage at a reasonable cost or in sufficient amounts to protect us against losses due to liability. If we obtain marketing approval for any of our product candidates, we intend to acquire insurance coverage to include the sale of commercial products; however, we may be unable to obtain product liability insurance on commercially reasonable terms or in adequate amounts. A successful product liability claim or series of claims brought against us could cause our share price to decline and, if judgments exceed our insurance coverage, could adversely affect our results of operations and business, including preventing or limiting the commercialization of any product candidates we develop.

We also expect that operating as a public company will make it more difficult and more expensive for us to obtain director and officer liability insurance, and we may be required to accept reduced policy limits and coverage or incur substantially higher costs to obtain the same or similar coverage. As a result, it may be more difficult for us to attract and retain qualified people to serve on our board of directors, our board committees or as executive officers. We do not know, however, if we will be able to maintain existing insurance with adequate levels of coverage. Any significant uninsured liability may require us to pay substantial amounts, which would adversely affect our cash position and results of operations.

Risks Related to Commercialization

We face significant competition from other biotechnology and pharmaceutical companies and our operating results will suffer if we fail to compete effectively.

The biopharmaceutical industry is characterized by intense competition and rapid innovation. Our competitors may be able to develop other compounds or drugs that are able to achieve similar or better results than those achieved by our product candidates. Our potential competitors include major multinational pharmaceutical companies, established biotechnology companies, specialty pharmaceutical companies and universities and other research institutions. Many of our competitors have substantially greater financial, technical and other resources, such as larger research and development staff, experienced marketing and manufacturing organizations and well-established sales forces. Smaller or early-stage companies may also prove to be significant competitors, particularly as they develop novel approaches to treating disease indications that our product candidates are also focused on treating. Established pharmaceutical companies may also invest heavily to accelerate discovery and development of novel therapeutics or to in-license novel therapeutics that could make the product candidates that we develop obsolete. Mergers and acquisitions in the biotechnology and pharmaceutical industries may result in even more resources being concentrated in our competitors. Competition may increase further as a result of advances in the commercial applicability of technologies and greater availability of capital for investment in these industries. Our competitors, either alone or with collaboration partners, may succeed in developing, acquiring or licensing on an exclusive basis drug or biologic products that are more effective, safer, more easily commercialized or less costly than our product candidates or may develop proprietary technologies or secure patent protection that we may need for the development of our technologies and products.

We consider our most direct competitors with respect to AL101 and AL102 to be companies developing gamma secretase inhibitors, including SpringWorks Therapeutics, Inc. and Celgene Corporation, recently acquired by BMS, or companies that develop Notch inhibitors, including Cellestia Biotech AG and Ciclomed LLC. In addition, with respect to AL101 for the treatment of ACC, we are aware that other companies are, or may be, developing products for this indication, including GlaxoSmithKline plc, Cellestia Biotech AG and LSK BioPartners, Inc. We believe the key competitive factors that will affect the development and commercial success of our product candidates are efficacy, safety, tolerability and reliability, convenience of use, price and reimbursement.

Even if we obtain regulatory approval of our product candidates, the availability and price of our competitors' products could limit the demand and the price we are able to charge for our product candidates. We may not be able to implement our business plan if the acceptance of our product candidates is inhibited by price competition or the reluctance of physicians to switch from existing methods of treatment to our product candidates, or if physicians switch to other new drug or biologic products or choose to reserve our product candidates for use in limited circumstances. For additional information regarding our competition, see "Business—Competition."

The successful commercialization of AL101, AL102 and any other product candidate we develop will depend in part on the extent to which governmental authorities and health insurers establish adequate coverage, reimbursement levels, and pricing policies. Failure to obtain or maintain coverage and adequate reimbursement for our product candidates, if approved, could limit our ability to market those products and decrease our ability to generate revenue.

The availability and adequacy of coverage and reimbursement by governmental healthcare programs such as Medicare and Medicaid, private health insurers and other third-party payors are essential for most patients to be able to afford prescription medications such as AL101 and AL102, if approved. Our ability to achieve acceptable levels of coverage and reimbursement for products by governmental authorities, private health insurers and other organizations will have an effect on our ability to successfully commercialize AL101, AL102 and any other product candidates we develop. Assuming we obtain coverage for our product candidates by a third-party payor, the resulting reimbursement payment rates may not be adequate or may require co-payments that patients find unacceptably high. We cannot be sure that coverage and reimbursement in the United States or elsewhere will be available for our product candidates or any product that we may develop, and any reimbursement that may become available may be decreased or eliminated in the future.

Third-party payors increasingly are challenging prices charged for pharmaceutical products and services, and many third-party payors may refuse to provide coverage and reimbursement for particular drugs or biologics when an equivalent generic drug, biosimilar, or a less expensive therapy is available. It is possible that a third-party payor may consider our product candidates as substitutable and only offer to reimburse patients for the less expensive product. Even if we show improved efficacy or improved convenience of administration with our product candidates, pricing of existing drugs may limit the amount we will be able to charge for our product candidates. Increasingly, other third-party payors are requiring that drug companies provide them with predetermined discounts from list prices and are challenging the prices charged for medical products. For products administered under the supervision of a physician, obtaining coverage and adequate reimbursement may be particularly difficult because of the higher prices often associated with such drugs. These payors may deny or revoke the reimbursement status of a given product or establish prices for new or existing marketed products at levels that are too low to enable us to realize an appropriate return on our investment in our product candidates. If reimbursement is not available or is available only at limited levels, we may not be able to successfully commercialize our product candidates and may not be able to obtain a satisfactory financial return on our product candidates.

There is significant uncertainty related to the insurance coverage and reimbursement of newly approved products. In the United States, third-party payors, including private and governmental payors, such as the Medicare and Medicaid programs, play an important role in determining the extent to which new drugs and biologics will be covered. The Medicare and Medicaid programs increasingly are used as models in the United States for how private payors and other governmental payors develop their coverage and reimbursement policies for drugs and biologics. Some third-party payors may require pre-approval of coverage for new or innovative devices or drug therapies before they will reimburse healthcare providers who use such therapies. It is difficult to predict at this time what third-party payors will decide with respect to the coverage and reimbursement for our product candidates.

No uniform policy for coverage and reimbursement for products exists among third-party payors in the United States. Therefore, coverage and reimbursement for products can differ significantly from payor to payor. As a result, the coverage determination process is often a time-consuming and costly process that will require us to provide scientific and clinical support for the use of our product candidates to each payor separately, with no assurance that coverage and adequate reimbursement will be applied consistently or obtained in the first instance. Furthermore, rules and regulations regarding reimbursement change frequently, in some cases at short notice, and we believe that changes in these rules and regulations are likely.

Outside the United States, international operations are generally subject to extensive governmental price controls and other market regulations, and we believe the increasing emphasis on cost-containment initiatives in Europe and other countries have and will continue to put pressure on the pricing and usage of our product candidates. In many countries, the prices of medical products are subject to varying price control mechanisms as part of the national health systems. Other countries allow companies to fix their own prices for medical products, but monitor and control company profits. Additional foreign price controls or other changes in pricing regulation could restrict the amount that we are able to charge for our product candidates. Accordingly, in markets outside the United States, the reimbursement for our product candidates may be reduced compared with the United States and may be insufficient to generate commercially reasonable revenue and profits.

Moreover, increasing efforts by governmental and third-party payors in the United States to cap or reduce healthcare costs may cause such organizations to limit both coverage and the level of reimbursement for newly approved products and, as a result, they may not cover or provide adequate payment for our product candidates. We expect to experience pricing pressures in connection with the sale of our product candidates due to the trend toward managed healthcare, the increasing influence of health maintenance organizations and additional legislative changes. The downward pressure on healthcare costs in general, particularly prescription drugs and other treatments, has become intense. As a result, increasingly high barriers are being erected to the entry of new products.

Even if AL101, AL102 or any other product candidate we develop receives marketing approval, it may fail to achieve market acceptance by physicians, patients, third-party payors or others in the medical community necessary for commercial success.

If AL101, AL102 or any other product candidate we develop receives marketing approval, it may nonetheless fail to gain sufficient market acceptance by physicians, patients, third-party payors and others in the medical community. If it does not achieve an adequate level of acceptance, we may not generate significant product revenues or become profitable. The degree of market acceptance of our product candidates, if approved, will depend on a number of factors, including but not limited to:

- the efficacy and potential advantages compared to alternative treatments;
- effectiveness of sales and marketing efforts;
- the cost of treatment in relation to alternative treatments, including any similar generic treatments;
- our ability to offer our products for sale at competitive prices;
- the convenience and ease of administration compared to alternative treatments;
- the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies;
- the strength of marketing and distribution support;
- the timing of market introduction of competitive products;
- the availability of third-party coverage and adequate reimbursement;
- product labeling or product insert requirements of the FDA, EMA or other regulatory authorities, including any limitations on warnings contained in a product's approved labeling;
- the prevalence and severity of any side effects; and
- any restrictions on the use of our product together with other medications.

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 and could require us to seek additional financing.

If we are unable to establish sales, marketing and distribution capabilities either on our own or in collaboration with third parties, we may not be successful in commercializing AL101 and AL102, if approved.

We do not have any infrastructure for the sales, marketing or distribution of AL101 and AL102, and the cost of establishing and maintaining such an organization may exceed the cost-effectiveness of doing so. In order to market and successfully commercialize AL101, AL102 or any other product candidate we develop, if approved, we must build our sales, distribution, marketing, managerial and other non-technical capabilities or make arrangements with third parties to perform these services. We expect to build a focused sales, distribution and marketing infrastructure to market AL101 and AL102, if approved. There are significant expenses and risks involved with establishing our own sales, marketing and distribution capabilities, including our ability to hire, retain and appropriately incentivize qualified individuals, generate sufficient sales leads, provide adequate training to sales and marketing personnel and effectively manage a geographically dispersed sales and marketing team. Any failure or delay in the development of our internal sales, marketing and distribution capabilities could delay any product launch, which would adversely impact the commercialization of that product. Additionally, if the commercial launch of AL101 or AL102 for which we recruit a sales force and establish marketing capabilities is delayed or does not occur for any reason, we would have prematurely or unnecessarily incurred these commercialization expenses. This may be costly, and our investment would be lost if we cannot retain or reposition our sales and marketing personnel.

Factors that may inhibit our efforts to commercialize our product candidates on our own include:

- our inability to recruit, train and retain adequate numbers of effective sales and marketing personnel;
- the inability of sales personnel to obtain access to physicians or attain adequate numbers of physicians to prescribe our products; and
- unforeseen costs and expenses associated with creating an independent sales and marketing organization.

We do not anticipate having the resources in the foreseeable future to allocate to the sales and marketing of our product candidates, if approved, in certain markets overseas. Therefore, our future success will depend, in part, on our ability to enter into and maintain collaborative relationships for such capabilities, the collaborator's strategic interest in a product and such collaborator's ability to successfully market and sell the product. We intend to pursue collaborative arrangements regarding the sale and marketing of AL101 and AL102, if approved, for certain markets overseas; however, we cannot assure you that we will be able to establish or maintain such collaborative arrangements, or if able to do so, that they will have effective sales forces. To the extent that we depend on third parties for marketing and distribution, any revenues we receive will depend upon the efforts of such third parties, and there can be no assurance that such efforts will be successful.

If we are unable to build our own sales force or negotiate a collaborative relationship for the commercialization of AL101 and AL102, we may be forced to delay the potential commercialization of AL101 and AL102 or reduce the scope of our sales or marketing activities for AL101 or AL102. If we need to increase our expenditures to fund commercialization activities for AL101 and AL102, we will need to obtain additional capital, which may not be available to us on acceptable terms, or at all. We may also have to enter into collaborative arrangements for AL101 and AL102 at an earlier stage than otherwise would be ideal and we may be required to relinquish rights to AL101 and AL102 or otherwise agree to terms unfavorable to us. Any of these occurrences may have an adverse effect on our business, operating results and prospects.

If we are unable to establish adequate sales, marketing and distribution capabilities, either on our own or in collaboration with third parties, we will not be successful in commercializing our product candidates and may never become profitable. We will be competing with many companies that currently have extensive and well-funded marketing and sales operations. 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.

A variety of risks associated with operating internationally could materially adversely affect our business.

Our principal executive offices are located in Israel and certain of our product candidates may be manufactured at third-party facilities located in the United States, UK, India and Australia. In addition, our business strategy includes potentially expanding internationally if any of our product candidates receives regulatory approval. Doing business internationally involves a number of risks, including but not limited to:

- multiple, conflicting and changing laws and regulations, such as privacy regulations, tax laws, export and import restrictions, employment laws, regulatory requirements and other governmental approvals, permits and licenses;
- failure by us to obtain and maintain regulatory approvals for the use of our products in various countries;
- additional potentially relevant third-party patent rights;
- complexities and difficulties in obtaining protection and enforcing our intellectual property;
- difficulties in staffing and managing foreign operations;
- complexities associated with managing multiple payor reimbursement regimes, government payors or patient self-pay systems;
- limits in our ability to penetrate international markets;
- global macroeconomic conditions, including inflation, labor shortages, supply chain shortages, or other economic, political or legal uncertainties or adverse developments;
- financial risks, such as longer payment cycles, difficulty collecting accounts receivable, the impact of local and regional financial crises on demand and payment for our products and exposure to foreign currency exchange rate fluctuations;
- political unrest, terrorism and wars, such as the current situation with Ukraine and Russia, which could delay or disrupt our business, and if such political unrest escalates or spills over to or otherwise impacts additional regions it could heighten many of the other risk factors included in this Item 1A;
- natural disasters and economic instability, including outbreak of disease, boycotts, curtailment of trade and other business restrictions;
- certain expenses including, among others, expenses for travel, translation and insurance; and
- regulatory and compliance risks that relate to maintaining accurate information and control over sales and activities that may fall within the purview of the U.S. Foreign Corrupt Practices Act, its books and records provisions, or its anti-bribery provisions.

Any of these factors could significantly harm our international expansion and operations and, consequently, our results of operations.

Risks Related to Our Dependence on Third Parties

Our employees and independent contractors, including principal investigators, CROs, consultants, vendors, and any third parties we may engage in connection with development and commercialization may engage in misconduct or other improper activities, including noncompliance with regulatory standards and requirements, which could have a material adverse effect on our business.

Our employees and independent contractors, including principal investigators, consultants, vendors and any third parties we may engage in connection with development and commercialization of our product candidates, could engage in misconduct, including intentional, reckless or negligent conduct or unauthorized activities that violate the laws and regulations of the FDA or other similar regulatory requirements of other authorities, including those laws that require the reporting of true, complete and accurate information to such authorities; manufacturing standards; data privacy, security, fraud and abuse and other healthcare laws and regulations; or laws that require the reporting of true, complete and accurate financial information and data. Specifically, sales, marketing and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, misconduct, kickbacks, self-dealing and other abusive practices. These laws and regulations may restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. Activities subject to these laws could also involve the improper use or misrepresentation of information obtained in the course of clinical trials, creation of fraudulent data in preclinical studies or clinical trials or illegal misappropriation of drug product, which could result in regulatory sanctions and cause serious harm to our reputation. It is not always possible to identify and deter misconduct by employees and other third parties, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to comply with such laws or regulations. Additionally, we are subject to the risk that a person or government could allege such fraud or other misconduct, even if none occurred. If any such actions are instituted against us and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business and results of operations, including the imposition of significant civil, criminal and administrative penalties, damages, monetary fines, disgorgements, possible exclusion from participation in Medicare, Medicaid, other U.S. federal healthcare programs or healthcare programs in other jurisdictions, individual imprisonment, other sanctions, contractual damages, reputational harm, diminished profits and future earnings, and curtailment of our operations.

We currently rely on third-party contract manufacturing organizations, or CMOs, for the production of clinical supply of AL101 and AL102 and intend to rely on CMOs for the production of commercial supply of AL101 and AL102, if approved. Our dependence on CMOs may impair the development of AL101 and AL102 and may impair the commercialization of AL101 and AL102, if approved, which would adversely impact our business and financial position.

We have limited personnel with experience in manufacturing, and we do not own facilities for manufacturing AL101, AL102 or any product candidate. Instead, we rely on and expect to continue to rely on CMOs for the supply of cGMP-grade clinical trial materials and commercial quantities of AL101, AL102 and any future product candidates, if approved. Reliance on CMOs may expose us to more risk than if we were to manufacture our product candidates ourselves. We plan to rely on CMOs to provide a sufficient clinical and commercial supply of AL101 and AL102.

The facilities used to manufacture our product candidates must be inspected by the FDA and comparable foreign authorities. While we provide oversight of manufacturing activities, we do not and will not control the execution of manufacturing activities by, and are or will be essentially dependent on, our CMOs for compliance with cGMP or similar foreign requirements outside the United States for the manufacture of our product candidates. As a result, we are subject to the risk that our product candidates may have manufacturing defects that we have limited ability to prevent. CMOs may also have competing obligations that prevent them from manufacturing our product candidates in a timely manner. If a CMO cannot successfully manufacture material that conforms to our specifications and the regulatory requirements, we will not be able to secure or maintain regulatory approval for the use of our product candidates in clinical trials, or for commercial distribution of our product candidates, if approved. In addition, we have limited control over the ability of our CMOs to maintain adequate quality control, quality assurance and qualified personnel. If the FDA or comparable foreign regulatory authority finds deficiencies with or does not approve these facilities for the manufacture of our product candidates or if it withdraws any such approval or finds deficiencies in the future, we may need to find alternative manufacturing facilities, which would delay our development program and significantly impact our ability to develop, obtain regulatory approval for or commercialize our product candidates, if approved. In addition, any failure to achieve and maintain compliance with these laws, regulations and standards could subject us to the risk that we may have to suspend the manufacture of our product candidates or that obtained approvals could be revoked. Furthermore, CMOs may breach existing agreements they have with us because of factors beyond our control. They may also terminate or refuse to renew their agreement at a time that is costly or otherwise inconvenient for us. If we were unable to find an adequate CMO or another acceptable solution in time, our clinical trials could be delayed or our commercial activities could be harmed.

We rely on and will continue to rely on CMOs to purchase from third-party suppliers the raw materials necessary to produce our product candidates. We do not and will not have control over the process or timing of the acquisition of these raw materials by our CMOs. The COVID-19 pandemic may also have an impact on the ability of our CMOs to acquire raw materials. Moreover, we currently do not have any agreements for the production of these raw materials. Supplies of raw materials could be interrupted from time to time and we cannot be certain that alternative supplies could be obtained within a reasonable time frame, at an acceptable cost, or at all. In addition, a disruption in the supply of raw materials could delay the commercial launch of our product candidates, if approved, or result in a shortage in supply, which would impair our ability to generate revenues from the sale of our product candidates. Growth in the costs and expenses of raw materials may also impair our ability to cost effectively manufacture our product candidates. There are a limited number of suppliers for the raw materials that we may use to manufacture our product candidates and we may need to assess alternative suppliers to prevent a possible disruption of the manufacture of our product candidates. Moreover, our product candidates utilize drug substances that are produced on a small scale, which could limit our ability to reach agreements with alternative suppliers.

Finding new CMOs or third-party suppliers involves additional cost and requires our management's time and focus. In addition, there is typically a transition period when a new CMO commences work. Although we generally have not, and do not intend to, begin a clinical trial unless we believe we have on hand, or will be able to obtain, a sufficient supply of our product candidates to complete the clinical trial, any significant delay in the supply of our product candidates or the raw materials needed to produce our product candidates, could considerably delay conducting our clinical trials and potential regulatory approval of our product candidates.

As part of their manufacture of our product candidates, our CMOs and third-party suppliers are expected to comply with and respect the intellectual property and proprietary rights of others. If a CMO or third-party supplier fails to acquire the proper licenses or otherwise infringes, misappropriates or otherwise violates the intellectual property or proprietary rights of others in the course of providing services to us, we may have to find alternative CMOs or third-party suppliers or defend against applicable claims, either of which would significantly impact our ability to develop, obtain regulatory approval for or commercialize our product candidates, if approved. Further, the extent to which the COVID-19 pandemic impacts our ability to procure sufficient supplies for the development of our product candidates will depend on the severity and duration of the spread of the virus, and the actions undertaken to contain COVID-19 or treat its effects.

We are dependent on a small number of suppliers for some of the materials used to manufacture our product candidates, and on one company for the manufacture of the active pharmaceutical ingredient for each of our product candidates.

We currently depend on a small number of suppliers for some of the materials used in, and processes required to develop, our product candidates. We cannot ensure that these suppliers or service providers will remain in business or have sufficient capacity or supply to meet our needs, or that they will not be purchased by one of our competitors or another company that is not interested in continuing to work with us. Our use of a small number of suppliers exposes us to several risks, including disruptions in supply, price increases or late deliveries. There are, in general, relatively few alternative sources of supply for substitute materials. Our current vendors may be unable or unwilling to meet our future demands for our clinical trials or commercial sale. Finding suitable replacement suppliers, materials and processes could take a substantial amount of time and it may be difficult to establish replacement suppliers who meet regulatory requirements. Any disruption or delay in supply could compromise our ability to pursue development and eventual commercialization of our product candidates.

We intend to rely on third parties to conduct, supervise and monitor our clinical trials. If those third parties do not successfully carry out their contractual duties, or if they perform in an unsatisfactory manner, it may harm our business.

We rely, and will continue to rely, on CROs, CRO-contracted vendors and clinical trial sites to ensure the proper and timely conduct of our clinical trials. Our reliance on CROs for clinical development activities limits our control over these activities, but we remain responsible for ensuring that each of our trials is conducted in accordance with the applicable protocol and legal, regulatory and scientific standards.

We and our CROs will be required to comply with the Good Laboratory Practice requirements for our preclinical studies and GCP requirements for our clinical trials, which are regulations and guidelines enforced by the FDA and are also required by comparable foreign regulatory authorities. Regulatory authorities enforce GCP requirements through periodic inspections of trial sponsors, principal investigators and clinical trial sites. If we or our CROs fail to comply with GCP requirements, 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. We cannot assure you that upon inspection by a given regulatory authority, such regulatory authority will determine that any of our clinical trials complies with GCP requirements.

In addition, our clinical trials must be conducted with product produced under cGMP or similar requirements outside the United States. Accordingly, if our CROs fail to comply with these requirements, we may be required to repeat clinical trials, which would delay the regulatory approval process. Moreover, our business may be adversely affected if any of these third parties violates federal or state fraud and abuse or false claims laws and regulations or healthcare privacy and security laws.

Our CROs are not our employees, and we do not control whether or not they devote sufficient time and resources to our clinical trials. Our 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 affect their performance on our behalf. 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 CROs do not successfully carry out their contractual duties or obligations, fail to meet expected deadlines, 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 reason, 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.

If our relationship with any 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's time and focus. In addition, there is a natural transition period when a new CRO commences work. As a result, delays occur, which can materially impact our ability to meet our desired clinical development timelines. Though 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 an adverse impact on our business, financial condition and prospects.

Our existing collaboration with Novartis is, and any future collaborations will be, important to our business. If we are unable to maintain our existing collaboration or enter into new collaborations, or if these collaborations are not successful, our business could be adversely affected.

An important part of our strategy is to evaluate and, as deemed appropriate, extend our current or enter into additional partnerships in the future, including potentially with major biopharmaceutical companies. We have limited capabilities for product development and do not yet have any capability for commercialization. Accordingly, we have entered into an evaluation, option and license agreement with Novartis, or the Novartis Agreement, that provides Novartis with the exclusive ability to evaluate, develop, and potentially license, AL102 in combination with Novartis' BCMA-targeting agents for the treatment of MM. For more information regarding the Novartis Agreement, please see "Business—License Agreements." We may also enter into collaborations with other companies to provide us with important technologies or funding for our programs.

Any current or future collaborations we may extend or enter into may pose a number of risks, including the following:

- collaborators have significant discretion in determining the efforts and resources that they will apply to these collaborations;
- collaborators may not perform their obligations as expected;
- collaborators may not pursue development and commercialization of any product candidates that achieve regulatory approval or may elect not to continue or renew development or commercialization programs based on preclinical study or clinical trial results, changes in the collaborators' strategic focus or available funding, or external factors, such as an acquisition, that divert resources or create competing priorities;
- collaborators may delay clinical trials, provide insufficient funding for a clinical trial program, stop a clinical trial or abandon a product candidate, repeat or conduct new clinical trials or require a new formulation of a product candidate for clinical testing;
- collaborators could independently develop, or develop with third parties, products that compete directly or indirectly with our product candidates if the collaborators believe that competitive products are more likely to be successfully developed or can be commercialized under terms that are more economically attractive than ours, which may cause collaborators to cease to devote resources to the commercialization of our product candidates;

- for collaborations involving combination therapies that have not yet been tested together, treatment emergent adverse events may be unforeseen and may negatively impact the development of our product candidates;

- collaborators may fail to comply with applicable regulatory requirements regarding the development, manufacture, distribution or marketing of a product candidate or product;

- a collaborator with marketing and distribution rights to one or more of our product candidates that achieve regulatory approval may not commit sufficient resources to the marketing and distribution of such product or products;

- disagreements with collaborators, including disagreements over proprietary rights, contract interpretation or the preferred course of development, might cause delays or termination of the research, development or commercialization of product candidates, might lead to additional responsibilities for us with respect to product candidates, or might result in litigation or arbitration, any of which would be time-consuming and expensive;

- collaborators may not properly obtain, maintain, enforce or defend our intellectual property rights or proprietary rights or may use our proprietary information in such a way as to invite litigation that could jeopardize or invalidate our intellectual property or proprietary information or expose us to potential litigation;

- collaborators may infringe, misappropriate or otherwise violate the intellectual property or proprietary rights of third parties, which may expose us to litigation and potential liability;

- collaborations may be terminated for the convenience of the collaborator and, if terminated, we would potentially lose the right to pursue further development or commercialization of the applicable product candidates;

- collaborators may learn about our technology and use this knowledge to compete with us in the future;

- there may be conflicts between different collaborators that could negatively affect those collaborations and potentially others;

- the number and type of our collaborations could adversely affect our attractiveness to future collaborators or acquirers; and

- the loss of, or a disruption in our relationship with, any one or more collaborators could harm our business.

Under the Novartis Agreement, the combination of AL102 with BCMA-targeting agents for the treatment of MM is currently being developed. Under the Novartis Agreement, upon completion of the relevant evaluation studies, we and Novartis will negotiate in good faith to provide for the expansion of the respective clinical collaboration and the establishment of a commercial relationship. However, Novartis has no obligation to continue development of the combination products, regardless of the applicable evaluation studies results.

If any collaborations do not result in the successful development and commercialization of products or if one of our collaborators terminates its agreement with us, we may not receive any future research and development funding or milestone or royalty payments under such collaborations. If we do not receive the funding we expect under these agreements, our continued development of our product candidates could be delayed and we may need additional resources to develop additional product candidates. All of the risks relating to product development, regulatory approval and commercialization described in this Annual Report on Form 10-K also apply to the activities of any collaborators and there can be no assurance that our collaborations will produce positive results or successful products on a timely basis or at all.

Additionally, subject to its contractual obligations to us, if one of our collaborators is involved in a business combination or otherwise changes its business priorities, the collaborator might deemphasize or terminate the development or commercialization of our product candidates. If a collaborator terminates its agreement with us, we may find it more difficult to attract new collaborators and the perception of our business and our stock price could be adversely affected.

We may in the future collaborate with additional pharmaceutical and biotechnology companies for development and potential commercialization of our product candidates. We face significant competition in seeking appropriate collaborators. Our ability to reach a definitive agreement for a collaboration will depend, among other things, upon our assessment of the collaborator's resources and expertise, the terms and conditions of the proposed collaboration and the proposed collaborator's evaluation of a number of factors. If we are unable to reach agreements with suitable collaborators on a timely basis, on acceptable terms, or at all, we may have to curtail the development of a product candidate, reduce or delay its development program or one or more of our other development programs, delay its potential commercialization or reduce the scope of any sales or marketing activities, or increase our expenditures and undertake development or commercialization activities at our own expense. If we elect to fund and undertake development or commercialization activities on our own, we may need to obtain additional expertise and additional capital, which may not be available to us on acceptable terms or at all. If we fail to enter into collaborations and do not have sufficient funds or expertise to undertake the necessary development and commercialization activities, we may not be able to further develop our product candidates or bring them to market or continue to develop our programs, and our business may be materially and adversely affected.

If we fail to comply with our obligations in the agreements under which we in-license or acquire development or commercialization rights to products, technology or data from third parties, including those for AL101 and AL102, we could lose such rights that are important to our business.

In November 2017, we licensed rights to AL101 and AL102 pursuant to the BMS License Agreement. This agreement imposes on us, and additional agreements we may enter into with other parties in the future may impose on us, diligence, development and commercialization timelines, milestone and royalty payment, insurance and other obligations.

For example, in exchange for the rights granted to us under the BMS License Agreement, we are obligated to pay BMS up to a total of $16.5 million in milestone payments for the ultimate approval of AL101 for the treatment of ACC in addition to other milestone payments that we are required to pay upon the achievement of other clinical development and commercial milestones, royalty payments that could range from a high single-digit to a low teen percentage on net sales of products containing AL101 or AL102, as well as a portion of all consideration we receive in connection with the sublicense or assignment of any patent rights we licensed from BMS, ranging from a mid-teen to mid-double-digit percentage, depending on the development stage of the most advanced product candidate that is subject to the applicable sublicense or assignment. If we or any of our collaborators fail to comply with our obligations under the BMS License Agreement or other current or future agreements, BMS or counterparties to other agreements may have the right to terminate such agreements, in which event we might not be able to develop, manufacture or market any product candidate that is covered by these agreements, which could materially adversely affect the value of the product candidate being developed under any such agreement. Termination of these agreements or reduction or elimination of our rights under these agreements may result in our having to negotiate new or reinstated agreements with less favorable terms, or cause us to lose our rights under these agreements, including our rights to important intellectual property or technology, and we may be required to cease the development and commercialization of AL101 and AL102 and any future product candidates that are subject to such agreements.

License agreements may also require us to meet specified development thresholds to maintain the license, including establishing a set timeline for developing and commercializing products.

Disputes may arise regarding intellectual property subject to a licensing agreement, including:

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

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

Risks Related to Healthcare Laws and Other Legal Compliance Matters

Enacted and future healthcare legislation may increase the difficulty and cost for us to obtain marketing approval of and commercialize our product candidates, if approved, and may affect the prices we may set.

In the United States, EU, and other jurisdictions, there have been, and we expect there will continue to be, a number of legislative and regulatory changes and proposed changes to the healthcare system that could affect our future results of operations. 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, in March 2010, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, or collectively the ACA, was enacted, which substantially changed the way healthcare is financed by both governmental and private insurers. Among the provisions of the ACA, those of greatest importance to the pharmaceutical and biotechnology industries include the following:

- an annual, non-deductible fee payable by any entity that manufactures or imports certain branded prescription drugs and biologic agents (other than those designated as orphan drugs), which is apportioned among these entities according to their market share in certain government healthcare programs;
- a new Medicare Part D coverage gap discount program, in which manufacturers must agree to offer point-of-sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for the manufacturer's outpatient drugs to be covered under Medicare Part D;
- new requirements to report certain financial arrangements with physicians and teaching hospitals, including reporting "transfers of value" made or distributed to prescribers and other healthcare providers and reporting investment interests held by physicians and their immediate family members;
- an increase in the statutory minimum rebates a manufacturer must pay under the Medicaid Drug Rebate Program to 23.1% and 13.0% of the average manufacturer price for branded and generic drugs, respectively and an extension of the rebate program to individuals enrolled in Medicaid managed care organizations;
- a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted, or injected;
- expansion of eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to certain individuals with income at or below 133% of the federal poverty level, thereby potentially increasing a manufacturer's Medicaid rebate liability;
- a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research; and
- establishment of a Center for Medicare & Medicaid Innovation at the Centers for Medicare & Medicaid Services, or CMS, to test innovative payment and service delivery models to lower Medicare and Medicaid spending, potentially including prescription drug spending.

Since its enactment, there have been judicial, Congressional and executive branch challenges to certain aspects of the ACA. On June 17, 2021, the U.S. Supreme Court dismissed the most recent judicial challenge to the ACA without specifically ruling on the constitutionality of the ACA. Prior to the Supreme Court's decision, President Biden issued an executive order initiating a special enrollment period from February 15, 2021 through August 15, 2021 for purposes of obtaining health insurance coverage through the ACA marketplace. The executive order also instructed certain governmental agencies to review and reconsider their existing policies and rules that limit access to healthcare.

Other legislative changes have been proposed and adopted in the United States since the ACA was enacted. For example, the Budget Control Act of 2011, resulted in aggregate reductions of Medicare payments to providers of 2% per fiscal year. These reductions went into effect in April 2013 and, due to subsequent legislative amendments to the statute, will remain in effect through 2030, with the exception of a temporary suspension from May 1, 2020 through March 31, 2022 and a 1% reduction from April 1, 2022 through June 30, 2022, unless additional action is taken by Congress. In January 2013, the American Taxpayer Relief Act of 2012 was signed into law, which, among other things, further reduced Medicare payments to several types of providers, including hospitals, imaging centers and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. More recently, on March 11, 2021, President Biden signed the American Rescue Plan Act of 2021 into law, which eliminates the statutory Medicaid drug rebate cap, currently set at 100% of a drug's average manufacturer price, beginning January 1, 2024.

Additionally, the orphan drug tax credit was reduced as part of a broader tax reform. 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 request access to certain IND products that have completed a Phase 1 clinical trial and that are undergoing investigation for FDA approval. 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. These new laws or any other similar laws introduced in the future may result in additional reductions in Medicare and other healthcare funding, which could negatively affect our customers and accordingly, our financial operations.

Moreover, payment methodologies may be subject to changes in healthcare legislation and regulatory initiatives. For example, CMS may develop new payment and delivery models, such as bundled payment models. In addition, recently 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. 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 product candidates or additional pricing pressures.

Individual states in the United States have also become increasingly aggressive in passing legislation and implementing regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing. Legally-mandated price controls on payment amounts by third-party payors or other restrictions could harm our business, results of operations, financial condition and prospects. In addition, regional healthcare authorities and individual hospitals are increasingly using bidding procedures to determine what pharmaceutical products and which suppliers will be included in their prescription drug and other healthcare programs. This could reduce the ultimate demand for our product candidates or put pressure on our product pricing.

In the EU, similar political, economic and regulatory developments may affect our ability to profitably commercialize our product candidates, if approved. In addition to continuing pressure on prices and cost containment measures, legislative developments at the EU or member state level may result in significant additional requirements or obstacles that may increase our operating costs. The delivery of healthcare in the EU, including the establishment and operation of health services and the pricing and reimbursement of medicines, is almost exclusively a matter for national, rather than EU, law and policy. National governments and health service providers have different priorities and approaches to the delivery of healthcare and the pricing and reimbursement of products in that context. In general, however, the healthcare budgetary constraints in most EU member states have resulted in restrictions on the pricing and reimbursement of medicines by relevant health service providers. Coupled with ever-increasing EU and national regulatory burdens on those wishing to develop and market products, this could prevent or delay marketing approval of our product candidates, restrict or regulate post-approval activities and affect our ability to commercialize our product candidates, if approved.

In December 2021, Regulation No 2021/2282 on Health Technology Assessment, or HTA, amending Directive 2011/24/EU, was adopted. This regulation which entered into force in January 2022 intends to boost cooperation among EU member states in assessing health technologies, including new medicinal products, and providing the basis for cooperation at the EU level for joint clinical assessments in these areas. The regulation foresees a three-year transitional period and will permit EU member states to use common HTA tools, methodologies, and procedures across the EU, working together in four main areas, including joint clinical assessment of the innovative health technologies with the most potential impact for patients, joint scientific consultations whereby developers can seek advice from HTA authorities, identification of emerging health technologies to identify promising technologies early, and continuing voluntary cooperation in other areas. Individual EU member states will continue to be responsible for assessing non-clinical (e.g., economic, social, ethical) aspects of health technologies, and making decisions on pricing and reimbursement.

In markets outside of the United States and EU, reimbursement and healthcare payment systems vary significantly by country, and many countries have instituted price ceilings on specific products and therapies.

We cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative action in the United States, the EU or any other jurisdiction. If we or any third parties we may engage are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we or such third parties are not able to maintain regulatory compliance, our product candidates may lose any regulatory approval that may have been obtained and we may not achieve or sustain profitability.

Our business operations and current and future relationships with investigators, healthcare professionals, consultants, third-party payors, patient organizations, and customers will be subject to applicable healthcare regulatory laws, which could expose us to penalties.

Our business operations and current and future arrangements with investigators, healthcare professionals, consultants, third-party payors, patient organizations, and customers, may expose us to broadly applicable fraud and abuse and other healthcare laws and regulations. These laws may constrain the business or financial arrangements and relationships through which we conduct our operations, including how we research, market, sell and distribute our product candidates, if approved. Such laws include:

- the U.S. federal Anti-Kickback Statute, which prohibits, among other things, persons or entities from knowingly and willfully soliciting, offering, receiving, or providing any remuneration (including any kickback, bribe, or certain rebate), directly or indirectly, overtly or covertly, in cash or in kind, to induce or reward, or in return for, either the referral of an individual for, or the purchase, lease, order, or recommendation of, any good, facility, item, or service, for which payment may be made, in whole or in part, under U.S. federal and state healthcare programs such as Medicare and Medicaid. A person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation;

- the U.S. federal false claims and civil monetary penalties laws, including the civil False Claims Act, or FCA, which, among other things, impose criminal and civil penalties, including through civil whistleblower or qui tam actions, against individuals or entities for knowingly presenting, or causing to be presented, to the U.S. federal government, claims for payment or approval that are false or fraudulent, knowingly making, using or causing to be made or used, a false record or statement material to a false or fraudulent claim, or from knowingly making a false statement to avoid, decrease or conceal an obligation to pay money to the U.S. federal government. In addition, the government may assert that a claim including items and services resulting from a violation of the U.S. federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the FCA;

- the U.S. federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which imposes criminal and civil liability for, among other things, knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program, or knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false statement, in connection with the delivery of, or payment for, healthcare benefits, items or services; similar to the U.S. federal Anti-Kickback Statute, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation;

- the FDCA, which prohibits, among other things, the adulteration or misbranding of drugs, biologics and medical devices;

- the U.S. federal legislation commonly referred to as the Physician Payments Sunshine Act and its implementing regulations, which requires certain manufacturers of drugs, devices, biologics, and medical supplies that are reimbursable under Medicare, Medicaid, or the Children's Health Insurance Program to report annually to the government information related to certain payments and other transfers of value to physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors), certain non-physician practitioners (physician assistants, nurse practitioners, clinical nurse specialists, anesthesiologist assistants, certified registered nurse anesthetists and certified nurse midwives), and teaching hospitals, as well as ownership and investment interests held by the physicians described above and their immediate family members.

- analogous U.S. state laws and regulations, including: state anti-kickback and false claims laws, which may apply to our business practices, including but not limited to, research, distribution, sales, and marketing arrangements and claims involving healthcare items or services reimbursed by any third-party payor, including private insurers; state laws that require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the U.S. federal government, or otherwise restrict payments that may be made to healthcare providers and other potential referral sources; and state laws and regulations that require drug manufacturers to file reports relating to pricing and marketing information, which requires tracking gifts and other remuneration and items of value provided to healthcare professionals and entities; and

- similar healthcare laws and regulations in the EU and other jurisdictions, including reporting requirements detailing interactions with and payments to healthcare providers.

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

Actual or perceived failures to comply with applicable data protection, privacy and security laws, regulations, standards and other requirements could adversely affect our business, results of operations, and financial condition.

The global data protection landscape is rapidly evolving, and we are or may become subject to numerous state, federal and foreign laws, requirements and regulations governing the collection, use, disclosure, retention, and security of personal data, such as information that we may collect in connection with clinical trials in the United States and abroad. Implementation standards and enforcement practices are likely to remain uncertain for the foreseeable future, and we cannot yet determine the impact future laws, regulations, standards, or perception of their requirements may have on our business. This evolution may create uncertainty in our business, affect our ability to operate in certain jurisdictions or to collect, store, transfer use and share personal information, necessitate the acceptance of more onerous obligations in our contracts, result in liability or impose additional costs on us. The cost of compliance with these laws, regulations and standards is high and is likely to increase in the future. Any failure or perceived failure by us to comply with federal, state or foreign laws or regulation, our internal policies and procedures or our contracts governing our processing of personal information could result in negative publicity, government investigations and enforcement actions, claims by third parties and damage to our reputation, any of which could have a material adverse effect on our operations, financial performance and business.

As our operations and business grow, we may become subject to or affected by new or additional data protection laws and regulations and face increased scrutiny or attention from regulatory authorities. In the United States, HIPAA imposes, among other things, certain standards relating to the privacy, security, transmission and breach reporting of individually identifiable health information. Certain states have also adopted comparable privacy and security laws and regulations, which govern the privacy, processing and protection of health-related and other personal information. Such laws and regulations will be subject to interpretation by various courts and other governmental authorities, thus creating potentially complex compliance issues for us and our future customers and strategic partners. For example, the California Consumer Privacy Act of 2018, or the CCPA, went into effect on January 1, 2020. The CCPA creates individual privacy rights for California consumers and increases the privacy and security obligations of entities handling certain personal information. The CCPA provides for civil penalties for violations, as well as a private right of action for data breaches that is expected to increase data breach litigation. The CCPA may increase our compliance costs and potential liability, and many similar laws have been proposed at the federal level and in other states. Further, the California Privacy Rights Act, or the CPRA, recently passed in California. The CPRA will impose additional data protection obligations on covered businesses, including additional consumer rights processes, limitations on data uses, new audit requirements for higher risk data, and opt outs for certain uses of sensitive data. It will also create a new California data protection agency authorized to issue substantive regulations and could result in increased privacy and information security enforcement. The majority of the provisions will go into effect on January 1, 2023, and additional compliance investment and potential business process changes may be required. Similar laws have passed in Virginia and Colorado, and have been proposed in other states and at the federal level, reflecting a trend toward more stringent privacy legislation in the United States. In the event that we are subject to or affected by HIPAA, the CCPA, the CPRA or other domestic privacy and data protection laws, any liability from failure to comply with the requirements of these laws could adversely affect our financial condition.

If we conduct clinical trials or enter into research collaborations in the EEA, we may be subject to the General Data Protection Regulation, or GDPR, which imposes strict requirements for processing the personal data of individuals within the EEA. If our or our partners' or service providers' privacy or data security measures fail to comply with GDPR requirements, we may be subject to litigation, regulatory investigations, enforcement notices requiring us to change the way we use personal data and/or fines of up to €20 million or 4% of our total worldwide annual turnover of the preceding financial year, whichever is higher, as well as compensation claims by affected individuals, negative publicity, reputational harm and a potential loss of business and goodwill. Among other requirements, the GDPR regulates transfers of personal data subject to the GDPR to third countries that have not been found to provide adequate protection to such personal data, including the United States; in July 2020, the Court of Justice of the EU, or CJEU, limited how organizations could lawfully transfer personal data from the EU/EEA to the United States by invalidating the Privacy Shield for purposes of international transfers and imposing further restrictions on the use of standard contractual clauses, or SCCs. The European Commission issued revised SCCs on June 4, 2021 to account for the decision of the CJEU and recommendations made by the European Data Protection Board. The revised SCCs must be used for relevant new data transfers from September 27, 2021; existing standard contractual clauses arrangements must be migrated to the revised clauses by December 27, 2022. The new SCCs apply only to the transfer of personal data outside of the EEA and not the UK; the UK's Information Commissioner's Office launched a public consultation on its draft revised data transfers mechanisms in August 2021 and laid its proposal before Parliament, with the UK SCCs expected to come into force in March 2022, with a two-year grace period. There is some uncertainty around whether the revised clauses can be used for all types of data transfers, particularly whether they can be relied on for data transfers to non-EEA entities subject to the GDPR. As supervisory authorities issue further guidance on personal data export mechanisms, including circumstances where the SCCs cannot be used, and/or start taking enforcement action, we could suffer additional costs, complaints and/or regulatory investigations or fines, and/or if we are otherwise unable to transfer personal data between and among countries and regions in which we operate, it could affect the manner in which we provide our services, the geographical location or segregation of our relevant systems and operations, and could adversely affect our financial results.

Further, from January 1, 2021, companies have to comply with the GDPR and also the UK GDPR, or the UK GDPR, which, together with the amended UK Data Protection Act 2018, retains the GDPR in UK national law. The UK GDPR mirrors the fines under the GDPR, i.e., fines up to the greater of €20 million (£17.5 million) or 4% of global turnover. The relationship between the UK and the EU in relation to certain aspects of data protection law remains unclear, and it is unclear how UK data protection laws and regulations will develop in the medium to longer term, and how data transfers to and from the UK will be regulated in the long term. The European Commission has adopted an adequacy decision in favor of the UK, enabling data transfers from EU member states to the UK without additional safeguards. However, the UK adequacy decision will automatically expire in June 2025 unless the European Commission re-assesses and renews or extends that decision.

Although we work to comply with applicable laws, regulations and standards, our contractual obligations and other legal obligations, these requirements are evolving and may be modified, interpreted and applied in an inconsistent manner from one jurisdiction to another, and may conflict with one another or other legal obligations with which we must comply. Any failure or perceived failure by us or our employees, representatives, contractors, consultants, collaborators, or other third parties to comply with such requirements or adequately address privacy and security concerns, even if unfounded, could result in additional cost and liability to us, damage our reputation, and adversely affect our business and results of operations.

We are subject to environmental, health and safety laws and regulations, and we may become exposed to liability and substantial expenses in connection with environmental compliance or remediation activities.

Our operations, including our development, testing and manufacturing activities, are subject to numerous environmental, health and safety laws and regulations. These laws and regulations govern, among other things, the controlled use, handling, release and disposal of and the maintenance of a registry for, hazardous materials and biological materials, such as chemical solvents, human cells, carcinogenic compounds, mutagenic compounds and compounds that have a toxic effect on reproduction, laboratory procedures and exposure to blood-borne pathogens. If we fail to comply with such laws and regulations, we could be subject to fines or other sanctions.

As with other companies engaged in activities similar to ours, we face a risk of environmental liability inherent in our current and historical activities, including liability relating to releases of or exposure to hazardous or biological materials. Environmental, health and safety laws and regulations are becoming more stringent. We may be required to incur substantial expenses in connection with future environmental compliance or remediation activities, in which case, the production efforts of our third-party manufacturers or our development efforts may be interrupted or delayed.

We are subject to certain U.S. and foreign anti-corruption, anti-money laundering, export control, sanctions and other trade laws and regulations.

We can face serious consequences for violations.

Among other matters, U.S. and foreign anti-corruption, anti-money laundering, export control, sanctions and other trade laws and regulations, which are collectively referred to as Trade Laws, prohibit companies and their employees, agents, clinical research organizations, legal counsel, accountants, consultants, contractors and other partners from authorizing, promising, offering, providing, soliciting or receiving, directly or indirectly, corrupt or improper payments or anything else of value to or from recipients in the public or private sector. We have direct or indirect interactions with officials and employees of government agencies or government-affiliated hospitals, universities and other organizations. We also expect our non-U.S. activities to increase in time. We plan to engage third parties for clinical trials and/or to obtain necessary permits, licenses, patent registrations and other regulatory approvals and we can be held liable for the corrupt or other illegal activities of our personnel, agents or partners, even if we do not explicitly authorize or have prior knowledge of such activities. Additionally, in many other countries, the healthcare providers who prescribe pharmaceuticals are employed by their government, and the purchasers of pharmaceuticals are government entities; therefore, our dealings with these prescribers and purchasers are subject to regulation under the Trade Laws. Violations of Trade Laws can result in substantial criminal fines and civil penalties, imprisonment, the loss of trade privileges, debarment, tax reassessments, breach of contract and fraud litigation, reputational harm and other consequences.

Risks Related to Our Intellectual Property

If we fail to comply with our obligations under our existing intellectual property license with BMS and any future intellectual property licenses with third parties, we could lose rights that are important to our business, including the right to develop and commercialize the AL101 and AL102 product candidates.

We are party to a license agreement with BMS which gives us the right to practice certain issued patents to develop and commercialize AL101 and AL102 and methods of use thereof. We may enter into additional license agreements in the future. Our existing license agreements impose, and any future license agreements are likely to impose, various diligence, milestone payment, royalty, insurance and other obligations on us. Any uncured, material breach under these license agreements could result in the loss of our rights to practice such in-licensed intellectual property and could compromise our development and commercialization efforts for any current product candidates, including requiring us to cease the development and commercialization of AL101 and AL102, or future product candidates and methods of use thereof.

If we are unable to obtain, maintain, protect and enforce patent and other intellectual property protection for our technology and products or if the scope of the patent or other intellectual property protection obtained is not sufficiently broad, our competitors could develop and commercialize products and technology similar or identical to ours, and we may not be able to compete effectively in our markets.

We rely upon a combination of patents, trade secret protection and confidentiality agreements to protect the intellectual property related to our proprietary technologies, product candidate development programs and product candidates. 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 AL101, AL102 and any future product candidates. We seek to protect our proprietary position by filing or collaborating with our licensors to file patent applications in the United States and abroad related to our development programs and product candidates. The patent prosecution process is expensive, time-consuming and complex, and we and our collaborators may not be able to file, prosecute, maintain or enforce all necessary or desirable patent applications at a reasonable cost or in a timely manner. Moreover, the issuance, scope, validity, enforceability and commercial value of our patent rights are highly uncertain.

It is possible that we will fail to identify further patentable aspects of our research and development output before it is too late to obtain patent protection. Although we enter into confidentiality agreements with employees, consultants, CROs, contractors, manufacturers, advisors and other third parties who have access to our confidential information, any of these parties may breach the agreements and disclose such output before a patent application is filed, thereby jeopardizing our ability to seek patent protection. In addition, publications of discoveries in the scientific literature often lag behind the actual discoveries, and patent applications in the United States, EU and elsewhere are published approximately 18 months after the earliest filing for which priority is claimed, or in some cases not at all. Therefore, we cannot be certain that we were the first to make the inventions claimed in our owned or any licensed patents or pending patent applications, or that we were the first to file for patent protection of such inventions. The patent applications that we own, or in-license, may fail to result in issued patents with claims that provide further coverage of AL101, AL102 or any other product candidate or methods of use thereof in the United States or in other foreign countries. There is no assurance that all of the potentially relevant prior art relating to our patents and patent applications has been found, which can invalidate a patent or prevent a patent from issuing from a pending patent application. Additionally, any U.S. provisional patent application that we or our licensors file is not eligible to become an issued patent until, among other things, we file a non-provisional patent application within 12 months of filing the related provisional patent application. If we or our licensors do not timely file any non-provisional patent application, we may lose our priority date with respect to the provisional patent application and any patent protection on the inventions disclosed in the provisional patent application. Even if patents do successfully issue and even if such patents further cover AL101, AL102 or any future product candidate or methods of use thereof, third parties may challenge their validity, ownership, enforceability or scope, which may result in such patents being narrowed, invalidated, circumvented, or held unenforceable. Any successful challenge to these patents or any other patents owned by or licensed to us could deprive us of rights necessary for the successful commercialization of AL101, AL102 or the methods of use thereof, or any other product candidates that we may develop. Further, if we encounter delays in regulatory approvals, the period of time during which we could market a product candidate under patent protection could be reduced.

If the patent applications we own or have in-licensed with respect to our development programs and product candidates fail to issue, if their validity, breadth or strength of protection is threatened, or if they fail to provide meaningful exclusivity for AL101, AL102 or any future product candidate, it could dissuade companies from collaborating with us to develop product candidates, and threaten our ability to commercialize future product candidates. Any such outcome could have a material adverse effect on our business.

The patent position of biotechnology and pharmaceutical companies is highly uncertain, involves complex legal, scientific, and factual questions, and is characterized by the existence of large numbers of patents and frequent litigation based on allegations of patent or other intellectual property infringement, misappropriation or other violations. In addition, the laws of jurisdictions outside the United States may not protect our rights to the same extent as the laws of the United States. For example, European patent law restricts the patentability of methods of treatment of the human body more than United States law does. Changes in either the patent laws or interpretation of the patent laws in the United States and other countries may diminish our ability to protect our inventions or obtain, maintain, and enforce our intellectual property rights and, more generally, could affect the value of our patents or narrow the scope of our patent protection. 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 the issuance of patents, or may result in the issuance of patents which fail to protect our technology or products, in whole or in part, or which fail to effectively prevent others from commercializing competitive technologies and products.

The issuance of a patent is not conclusive as to its inventorship, ownership, scope, validity or enforceability, and we may be subject to a third-party pre-issuance submission of prior art, or our owned and licensed 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 freedom to operate or in patent claims being narrowed, invalidated or held unenforceable, in whole or in part, which could limit our ability to stop others from using or commercializing similar or identical technology and products, or limit the duration of the patent protection of our technology and products. Thus, even if our patent applications issue as patents, they may not issue in a form that will provide us with meaningful protection, prevent competitors from competing with us or otherwise provide us with any competitive advantage. Moreover, patents have a limited lifespan. In the United States, the natural expiration of a patent is generally 20 years after it is filed. Patent term extensions may be available; however the life of a patent, and the protection it affords, is limited. Without sufficient patent protection for our current or future product candidates, we may be open to competition from generic versions of such products. Our competitors or other third parties may also be able to circumvent our patents by developing similar or alternative technologies or products in a non-infringing manner.

In addition, given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized. Moreover, some of our owned and in-licensed patents and patent applications are, and may in the future be, co-owned with third parties. If we are unable to obtain an exclusive license to any such third party co-owners' interest in such patents or patent applications, such co-owners may be able to license their rights to other third parties, including our competitors, and our competitors could market competing products and technology. In addition, we may need the cooperation of any such co-owners of our patents in order to enforce such patents against third parties, and such cooperation may not be provided to us. As a result, our owned and licensed patent portfolio may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours. Any of the foregoing could have a material adverse effect on our business, financial condition, results of operations, and prospects.

Third parties may assert claims against us alleging infringement, misappropriation or other violation of their patents or other intellectual property rights, and we may need to become involved in lawsuits to protect or enforce our patents or other intellectual property rights, either of which could result in substantial costs or loss of productivity, delay or prevent the development and commercialization of our product candidates, prohibit our use of proprietary technology or sale of products or put our patents and other proprietary rights at risk.

Our commercial success depends, in part, upon our ability and the ability of our collaborators to develop, manufacture, market and sell our product candidates without alleged or actual infringement, misappropriation or other violations of the patents and proprietary rights of third parties. Litigation relating to infringement, misappropriation or other violation of patent and other intellectual property rights in the pharmaceutical and biotechnology industries is common, including patent infringement lawsuits, interferences, oppositions and post-grant review, *inter partes* review, reexamination and derivation proceedings before the U.S. Patent and Trademark Office, or USPTO, and corresponding foreign patent offices. The various markets in which we plan to operate are subject to frequent and extensive litigation regarding patents and other intellectual property rights, and 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. In addition, many companies in intellectual property-dependent industries, including the biotechnology and pharmaceutical industries, have employed intellectual property litigation as a means to gain an advantage over their competitors. Numerous U.S., EU and foreign issued patents and pending patent applications, which are owned by third parties, exist in the fields in which we are developing product candidates, and as the biotechnology and pharmaceutical industries expand and more patents are issued, the risk increases that our product candidates may be subject to claims of infringement, misappropriation or other violation of the intellectual property rights of third parties. Some claimants may have substantially greater resources than we do and may be able to sustain the costs of complex intellectual property litigation to a greater degree and for longer periods of time than we could. In addition, patent holding companies that focus solely on extracting royalties and settlements by enforcing patent rights may target us.

We may be subject to third-party claims including infringement, interference or derivation proceedings, post-grant review, *inter partes* review and reexamination proceedings before the USPTO or similar adversarial proceedings or litigation in other jurisdictions. In order to successfully challenge the validity of any such U.S. patent in federal courts, we would need to overcome a presumption of validity. As this burden is a high one requiring 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. Even if we believe such claims are without merit, a court of competent jurisdiction could hold that any such third-party patents are valid, enforceable and infringed, and the holders of any such patents may be able to block our ability to commercialize the applicable product candidate unless we obtained a license under the applicable patents, or until such patents expire or are finally determined to be invalid or unenforceable. Similarly, if any third-party patents were held by a court of competent jurisdiction to cover aspects of our compositions, formulations, or methods of treatment, prevention or use, the holders of any such patents may be able to prohibit our use of those compositions, formulations, methods of treatment, prevention or use or other technologies, effectively blocking our ability to develop and commercialize the applicable product candidate until such patent expires or is finally determined to be invalid or unenforceable or unless we obtained a license.

In addition, defending such claims would cause us to incur substantial expenses and, if successful, could cause us to pay substantial damages if we are found to be infringing a third party's patent or other intellectual property rights. These damages potentially include increased damages (possibly treble damages) and attorneys' fees if we are found to have infringed such rights willfully. Further, if a patent or other intellectual property infringement suit is brought against us or our third-party service providers, our development, manufacturing or sales activities relating to the product or product candidate that is the subject of the suit may be delayed or terminated, as parties making claims against us may obtain injunctive or other equitable relief. As a result of patent or other intellectual property infringement claims, or in order to avoid potential infringement claims, we may choose to seek, or be required to seek, a license from the third party in order to develop and commercialize the applicable product candidate, which may require payment of substantial royalties or fees, or require us to grant a cross-license under our intellectual property rights. These licenses may not be available on reasonable terms or at all. Even if a license can be obtained on reasonable terms, the rights may be non-exclusive, which would give our competitors access to the same intellectual property rights. If we are unable to enter into a license on acceptable terms, we could be prevented from commercializing one or more of our product candidates, or forced to modify such product candidates, or to cease some aspect of our business operations, which could harm our business significantly. We might also be forced to redesign or modify our product candidates so that we no longer infringe the third-party intellectual property rights, which may result in significant cost or delay to us, or which redesign or modification could be impossible or technically infeasible. Even if we were ultimately to prevail, any of these events could require us to divert substantial financial and management resources that we would otherwise be able to devote to our business. In addition, if the breadth or strength of protection provided the patents and patent applications we own or in-license is threatened, it could dissuade companies from collaborating with us to license, develop or commercialize current or future product candidates.

If we or one of our licensors or collaborators were to initiate legal proceedings against a third party to enforce an owned or in-licensed patent covering one of our product candidates, the defendant could counterclaim that such patent is invalid or unenforceable. In patent litigation in the United States and in Europe, defendant counterclaims alleging invalidity or unenforceability are commonplace, and a court may decide that a patent owned or in-licensed by us is invalid or unenforceable, or may refuse to stop the other party from using the technology at issue on the grounds that our owned and in-licensed patents do not cover the technology in question. Grounds for a validity challenge could be an alleged failure to meet any of several statutory requirements, for example, lack of novelty, obviousness or non-enablement. Third parties might allege unenforceability of our patents because during prosecution of the patent an individual connected with such prosecution withheld relevant information, or made a misleading statement. The outcome of proceedings involving assertions of invalidity and unenforceability during patent litigation is unpredictable. With respect to the validity of patents, for example, we cannot be certain that there is no invalidating prior art of which we and the patent examiner were unaware during prosecution, but that an adverse third party may identify and submit in support of such assertions of invalidity. If a defendant were to prevail on a legal assertion of invalidity or unenforceability, we would lose at least part, and perhaps all, of the patent protection on our product candidates. Our patents and other intellectual property rights also will not protect our technology if competitors design around our protected technology without infringing our patents or other intellectual property rights.

Even if resolved in our favor, litigation or other legal proceedings relating to intellectual property claims may cause us to incur significant expenses and could distract our technical and management personnel from their normal responsibilities. In addition, 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, and if securities analysts or investors view these announcements in a negative light, the price of our common stock could be adversely affected. Such litigation or proceedings could substantially increase our operating losses and reduce our resources available for development activities. We may not have sufficient financial or other resources to adequately conduct such litigation or proceedings. Some of our competitors may be able to sustain the costs of such litigation or proceedings more effectively than we can because of their substantially greater financial resources. 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. Any of the foregoing could have a material adverse effect on our business, financial condition, results of operations, and prospects.

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

We cannot guarantee that any of our or our licensors' patent searches or analyses, including but not limited to the identification of relevant patents, the scope of patent claims or the expiration of relevant patents, are complete or thorough, nor can we be certain that we have identified each and every third-party patent and pending application in the United States, Europe and elsewhere that is relevant to or necessary for the commercialization of our product candidates in any jurisdiction. Patent applications in the United States, EU and elsewhere are published approximately 18 months after the earliest filing for which priority is claimed, with such earliest filing date being commonly referred to as the priority date. Therefore, patent applications covering our product candidates could be filed by others without our knowledge. Additionally, pending patent applications that have been published can, subject to certain limitations, be later amended in a manner that could cover our product candidates or the use of our product candidates. After issuance, the scope of patent claims remains subject to construction as determined by an interpretation of the law, the written disclosure in a patent and the patent's prosecution history. Our interpretation of the relevance or the scope of a patent or a pending application may be incorrect, which may negatively impact our ability to market our product candidates. We may incorrectly determine that our product candidates or methods of use thereof are not covered by a third-party patent or may incorrectly predict whether a third party's pending application will issue with claims of relevant scope. Our determination of the expiration date of any patent in the United States, the EU or elsewhere that we consider relevant may be incorrect, which may negatively impact our ability to develop and market our product candidates. Our failure to identify and correctly interpret relevant patents may negatively impact our ability to develop and market our product candidates.

From time to time we may identify patents or applications in the same general area as our products and product candidates and methods of use thereof. We may determine these third-party patents are irrelevant to our business based on various factors including our interpretation of the scope of the patent claims and our interpretation of when the patent expires. If the patents are asserted against us, however, a court may disagree with our determinations. Further, while we may determine that the scope of claims that will issue from a patent application does not present a risk, it is difficult to accurately predict the scope of claims that will issue from a patent application, our determination may be incorrect, and the issuing patent may be asserted against us. We cannot guarantee that we will be able to successfully settle or otherwise resolve such infringement claims. If we fail in any such dispute, in addition to being forced to pay monetary damages, we may be temporarily or permanently prohibited from commercializing our product candidates or be required to obtain a license under such patent, which may not be available on reasonable terms or at all. We might, if possible, also be forced to redesign our product candidates so that we no longer infringe, misappropriate or otherwise violate the third-party intellectual property rights. Any of these events, even if we were ultimately to prevail, could require us to divert substantial financial and management resources that we would otherwise be able to devote to our business. Any of the foregoing could have a material adverse effect on our business, financial condition, results of operations, and prospects.

Changes in patent laws or patent jurisprudence could diminish the value of patents in general, thereby impairing our ability to protect our product candidates.

As is the case with other biopharmaceutical and pharmaceutical companies, our success is heavily dependent on intellectual property, particularly patents. Obtaining and enforcing patents in the biopharmaceutical and pharmaceutical industries involve both technological and legal complexity. Therefore, obtaining and enforcing biopharmaceutical and pharmaceutical patents is costly, time-consuming and inherently uncertain. In addition, the Leahy-Smith America Invents Act, or the AIA, which was passed in September 2011, resulted in significant changes to the U.S. patent system.

An important change introduced by the AIA is that, as of March 16, 2013, the United States transitioned from a “first-to-invent” to a “first-to-file” system for deciding which party should be granted a patent when two or more patent applications are filed by different parties claiming the same invention. Under a “first-to-file” system, assuming the other requirements for patentability are met, the first inventor to file a patent application generally will be entitled to a patent on the invention regardless of whether another inventor had made the invention earlier. A third party that files a patent application in the USPTO after that date but before us could therefore be awarded a patent covering an invention of ours even if we made the invention before it was made by the third party. This will require us to be cognizant of the time from invention to filing of a patent application and be diligent in filing patent applications, but circumstances could prevent us from promptly filing patent applications on our inventions.

Among some of the other changes introduced by the AIA are changes that limit where a patentee may file a patent infringement suit and providing opportunities for third parties to challenge any issued patent with the USPTO. This applies to all of our U.S. patents, even those issued before March 16, 2013. Because of a lower evidentiary standard in USPTO proceedings compared to the evidentiary standard in U.S. federal courts necessary to invalidate a patent claim, a third party could potentially provide evidence in a USPTO proceeding sufficient for the USPTO to hold a claim invalid even though the same evidence would be insufficient to invalidate the claim if first presented in a district court action.

Accordingly, a third party may attempt to use the USPTO procedures to invalidate our patent claims that would not have been invalidated if first challenged by the third party as a defendant in a district court action. It is not clear what, if any, impact the AIA will have on the operation of our business. However, the AIA and its implementation could increase the uncertainties and costs surrounding the prosecution of our or our licensors’ patent applications and the enforcement or defense of our or our licensors’ issued patents.

We may become involved in opposition, interference, derivation, *inter partes* review, post-grant review, reexamination or other proceedings challenging our or our licensors’ patent rights, and the outcome of any proceedings are highly uncertain. An adverse determination in any such proceeding could reduce the scope of, or invalidate, our owned or in-licensed patent rights, in whole or in part, allow third parties to commercialize our technology or products and compete directly with us, without payment to us, or result in our inability to manufacture or commercialize products without infringing third-party patent rights.

Additionally, 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 validity, enforceability and value of patents, once obtained. Depending on decisions by Congress, the federal courts and the USPTO, as well as similar bodies in other jurisdictions, the laws and regulations governing patents could change in unpredictable ways that could weaken our ability to obtain new patents or to enforce our existing patents and patents that we might obtain in the future. Similarly, the complexity and uncertainty of European patent laws have also increased in recent years. In addition, the European patent system is relatively stringent in the type of amendments that are allowed during prosecution. Complying with these laws and regulations could limit our ability to obtain new patents in the future that may be important for our business, and these laws and regulations patents could continue to change in unpredictable ways that could have a material adverse effect on our existing patent rights and our ability to protect and enforce our intellectual property in the future.

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

The USPTO and European and other 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, renewal and annuity fees on any issued patent are due to be paid to the USPTO and European and other patent agencies over the lifetime of a patent. While an inadvertent failure to make payment of such fees or to comply with such provisions can in many cases be cured by additional payment of a late fee or by other means in accordance with the applicable rules, there are situations in which such noncompliance will result in the abandonment or lapse of the patent or patent application, and the partial or complete loss of patent rights in the relevant jurisdiction. Non-compliance events that could result in abandonment or lapse of a patent or patent application include failure to respond to official actions within prescribed time limits, non-payment of fees and failure to properly legalize and submit formal documents within prescribed time limits. If we or our licensors fail to maintain the patents and patent applications covering our product candidates or if we or our licensors otherwise allow our patents or patent applications to be abandoned or lapse, our competitors might be able to enter the market, which would hurt our competitive position and could impair our ability to successfully commercialize our product candidates in any indication for which they are approved, which could have a material adverse effect on our business, financial condition, results of operations, and prospects.

We enjoy only limited geographical protection with respect to certain patents and we may not be able to protect our intellectual property and proprietary rights throughout the world.

Filing, prosecuting and defending patents covering our product candidates in all countries throughout the world would be prohibitively expensive, and our intellectual property rights in some countries outside the United States can be less extensive than those in the United States. In-licensing patents covering our product candidates in all countries throughout the world may similarly be prohibitively expensive, if such opportunities are available at all, and even in-licensing or filing, prosecuting and defending patents in only those jurisdictions in which we develop or commercialize our product candidates may still be prohibitively expensive or impractical. Competitors may use our and our licensors' technologies in jurisdictions where we have not obtained patent protection or licensed patents to develop their own products and, further, may export otherwise infringing products to territories where we and our licensors have patent protection, but enforcement is not as strong as that in the United States or the EU. These products may compete with our product candidates, and our or our licensors' patents or other intellectual property rights may not be effective or sufficient to prevent them from competing.

In addition, we may decide to abandon national and regional patent applications while they are still pending. The grant proceeding of each national or regional patent is an independent proceeding which may lead to situations in which applications may be rejected by the relevant patent office, while substantively similar applications are granted by others. For example, relative to other countries, China has a heightened requirement for patentability and specifically requires a detailed description of medical uses of a claimed drug. Furthermore, generic drug manufacturers or other competitors may challenge the scope, validity or enforceability of our or our licensors' patents, requiring us or our licensors to engage in complex, lengthy and costly litigation or other proceedings. Generic drug manufacturers may develop, seek approval for and launch generic versions of our products. It is also common for, depending on the country, the scope of patent protection to vary for the same product candidate or technology.

The laws of some jurisdictions do not protect intellectual property rights to the same extent as the laws or regulations in the United States and the EU, and many companies have encountered significant difficulties in protecting and defending proprietary rights in such jurisdictions. Moreover, the legal systems of certain countries, particularly certain developing countries, do not favor the enforcement of patents, trade secrets or other forms of intellectual property, which could make it difficult for us to prevent competitors in some jurisdictions from marketing competing products in violation of our proprietary rights generally. Proceedings to enforce our patent rights in foreign jurisdictions, whether or not successful, are likely to result in substantial costs and divert our efforts and attention from other aspects of our business, and additionally could put at risk our or our licensors' patents of being invalidated or interpreted narrowly, could increase the risk of our or our licensors' patent applications not issuing, or could provoke third parties to assert claims against us. We may not prevail in any lawsuits that we initiate, while damages or other remedies may be awarded to the adverse party, which may be commercially significant. If we prevail, damages or other remedies awarded to us, if any, may not be commercially meaningful. Accordingly, our efforts to enforce our intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop or license. Furthermore, while we intend to protect our intellectual property rights in our expected significant markets, we cannot ensure that we will be able to initiate or maintain similar efforts in all jurisdictions in which we may wish to market our product candidates. Accordingly, our efforts to protect our intellectual property rights in such countries may be inadequate, which may have an adverse effect on our ability to successfully commercialize our product candidates in all of our expected significant foreign markets. If we or our licensors encounter difficulties in protecting, or are otherwise precluded from effectively protecting, the intellectual property rights important for our business in such jurisdictions, the value of these rights may be diminished and we may face additional competition in those jurisdictions.

In some jurisdictions, compulsory licensing laws compel patent owners to grant licenses to third parties. In addition, some 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 are forced to grant a license to third parties under patents relevant to our business, or if we or our licensors are prevented from enforcing patent rights against third parties, our competitive position may be substantially impaired in such jurisdictions. Any of the foregoing could have a material adverse effect on our business, financial condition, results of operations, and prospects.

If we do not obtain patent term extension in the United States under the Hatch-Waxman Act and in foreign countries under similar legislation, thereby potentially extending the term of marketing exclusivity for our product candidates, our business may be materially harmed.

The term of any individual patent depends on applicable law in the country where the patent is granted. In the United States, provided all maintenance fees are timely paid, a patent generally has a term of 20 years from its application filing date or earliest claimed non-provisional filing date. Extensions may be available under certain circumstances, but the life of a patent and, correspondingly, the protection it affords is limited. Even if we or our licensors obtain patents covering our product candidates, when the terms of all patents covering a product expire, our business may become subject to competition from competitive medications, including generic medications. Given the amount of time required for the development, testing and regulatory review and approval of new product candidates, patents protecting such candidates may expire before or shortly after such candidates are commercialized. As a result, our owned and licensed patent portfolio may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours.

In the United States, a patent that covers an FDA-approved drug or biologic may be eligible for a term extension designed to restore the period of the patent term that is lost during the premarket regulatory review process conducted by the FDA. Depending upon the timing, duration and conditions of FDA marketing approval of our product candidates, one or more of our U.S. patents may be eligible for limited patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984, or the Hatch-Waxman Act, which permits a patent term extension of up to five years for a patent covering an approved product as compensation for effective patent term lost during product development and the FDA regulatory review process. While the length of such patent term extension is related to the length of time the drug is under regulatory review, patent term extension cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval, only one patent per approved drug may be extended and only those claims covering the approved drug product, a method for using it or a method for manufacturing it may be extended. In the EU, our product candidates may be eligible for patent term extensions based on similar legislation. In either jurisdiction, however, we may not receive an extension if we fail to apply within applicable deadlines, fail to apply prior to expiration of relevant patents, fail to exercise due diligence during the testing phase or regulatory review process or otherwise fail to satisfy applicable requirements. Even if we are granted such extension, the duration of such extension may be less than our request. If we are unable to obtain a patent term extension, or if the term of any such extension is less than our request, the period during which we can enforce our patent rights for that product will be in effect shortened and our competitors may obtain approval to market competing products sooner. The resulting reduction of years of revenue from applicable products could be substantial.

Further, under certain circumstances, patent terms covering our products or product candidates may be extended for time spent during the pendency of the patent application in the USPTO (referred to as patent term adjustment, or PTA). The laws and regulations underlying how the USPTO calculates the PTA is subject to change and any such PTA granted by the USPTO could be challenged by a third party. If we do not prevail under such a challenge, the PTA may be reduced or eliminated, resulting in a shorter patent term, which may negatively impact our ability to exclude competitors.

Because PTA added to the term of patents covering pharmaceutical products has particular value, our business may be adversely affected if the PTA is successfully challenged by a third party and our ability to exclude competitors is reduced or eliminated.

Our proprietary rights may not adequately protect our technologies and product candidates, and do not necessarily address all potential threats to our competitive advantage.

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

- others may be able to make products that are similar to AL101, AL102 or our future product candidates and methods of use thereof but that are not covered by the claims of the patents that we own or exclusively licensed;
- others, including inventors or developers of our owned or in-licensed patent technologies who may become involved with competitors, may independently develop similar or alternative technologies or otherwise circumvent any of our technologies without infringing our intellectual property rights;
- we or any of our collaborators might not have been the first to conceive and reduce to practice the inventions covered by the patents or patent applications that we own, license or will own or license;
- we or any of our collaborators might not have been the first to file patent applications covering certain of the patents or patent applications that we or they own, license or will own or license;
- it is possible that our pending patent applications will not lead to issued patents;
- it is possible that there are prior public disclosures that could invalidate our or our licensors' patents;
- issued patents that we own or exclusively license may not provide us with any competitive advantage, or may be held invalid or unenforceable, as a result of legal challenges by our competitors;

- our competitors might conduct research and development activities in countries where we do not have patent rights, or in countries where research and development safe harbor laws exist, and then use the information learned from such activities to develop competitive products for sale in our major commercial markets;

- ownership, validity or enforceability of our or our licensors' patents or patent applications may be challenged by third parties; and

- the patents of third parties or pending or future applications of third parties, if issued, may have an adverse effect on our business.

Any of the foregoing could have a material adverse effect on our business, financial condition, results of operations, and prospects.

Our reliance on third parties requires us to share our trade secrets, which increases the possibility that our trade secrets will be misappropriated or disclosed, and confidentiality agreements with employees and third parties may not adequately prevent disclosure of trade secrets and protect other proprietary information.

We consider proprietary trade secrets and confidential or unpatented know-how to be important to our business. We may rely on trade secrets or confidential know-how to protect our technology, especially where patent protection is believed by us to be of limited value. However, trade secrets and confidential know-how are difficult to protect, and we have limited control over the protection of trade secrets and confidential know-how used by our licensors, collaborators and suppliers. Because we expect to rely on third parties to manufacture AL101, AL102 and any future product candidates, and we expect to collaborate with third parties on the development of AL101, AL102 and any future product candidates, we must, at times, share trade secrets with them. We 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. Under such circumstances, trade secrets or confidential know-how can be difficult to maintain as confidential.

To protect this type of information against disclosure or appropriation by competitors, our policy is to require our employees, consultants, CROs, contractors, manufacturers, advisors and other third parties who have access to our confidential information to enter into confidentiality agreements and, if applicable, material transfer agreements, consulting agreements or other similar agreements with us prior to beginning research or us disclosing proprietary information. These agreements typically limit the rights of the third parties to use or disclose our confidential information, including our trade secrets. However, we cannot guarantee that we have entered into such agreements with each party that may have or have had access to our trade secrets or proprietary technology. Despite our efforts, any such parties may breach these agreements and unintentionally or willfully disclose our confidential information to competitors, and confidentiality agreements may not provide an adequate remedy in the event of unauthorized disclosure of confidential information. 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 competitive 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 would impair our competitive position and may have an adverse effect on our business and results of operations. Enforcing a claim that a third party obtained illegally or misappropriated trade secrets or confidential know-how is expensive, time consuming and unpredictable, and the enforceability of confidentiality agreements and the protection of trade secrets generally may vary from jurisdiction to jurisdiction.

In addition, our agreements typically restrict the ability of our advisors, employees, third-party contractors, consultants, CROs, manufacturers, advisors and other third parties to publish data potentially relating to our trade secrets, although the agreements may grant certain limited publication rights. Despite our efforts to protect our trade secrets, our competitors or other third parties may discover our trade secrets, either through breach of our agreements with third parties, independent development or publication of information by any of our third-party collaborators. A competitor's or other third party's discovery of our trade secrets would impair our competitive position and have a material adverse effect on our business.

We may need to license certain intellectual property from third parties, and such licenses may not be available or may not be available on commercially reasonable terms.

The growth of our business may depend in part on our ability to acquire or in-license additional intellectual property or proprietary rights. For example, our programs may involve product candidates that may require the use of additional intellectual property or proprietary rights held by third parties. Our product candidates may also require specific formulations to work effectively and efficiently, which may be covered by intellectual property rights held by others. We may also develop products containing combinations of our compositions and pre-existing pharmaceutical compositions, and could be required by the FDA or comparable foreign regulatory authorities to provide a companion diagnostic test or tests with our product candidates, both of which may also be covered by intellectual property rights held by others. We may be unable to acquire or in-license any relevant third-party intellectual property rights that we identify as necessary or important to our business operations at a reasonable cost or on reasonable terms, if at all. The licensing or acquisition of third-party intellectual property rights is a competitive area, and several more established companies may pursue strategies to license or acquire third-party intellectual property rights 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. In cases where we are unable to procure sufficient rights to third-party intellectual property rights, we might need to cease use of the compositions or methods covered by such third-party intellectual property rights and/or develop alternative approaches that do not infringe, misappropriate or otherwise violate such intellectual property rights. This could entail additional costs and development delays, and the development of such alternatives may not be feasible. Even if we are able to obtain a license under such intellectual property rights, any such license may be non-exclusive, which may allow our competitors access to the same technologies licensed to us. Any of the foregoing could prevent us from developing or commercializing one or more of our product candidates, or force us to modify such product candidates, or to cease some aspect of our business operations, which could have a material adverse effect on our business.

We may be subject to claims that our employees, consultants or independent contractors have wrongfully used or disclosed confidential information of their former employers or other third parties or claims asserting ownership of what we regard as our own intellectual property.

We do and may employ and contract with individuals who were previously employed by other biotechnology or pharmaceutical companies. Although we seek to protect our ownership of intellectual property rights by ensuring that our agreements with our employees, collaborators and other third parties with whom we do business include provisions requiring such parties to assign rights in inventions to us and to not use the know-how or confidential information of their former employer or other third parties, we cannot guarantee that we have executed such agreements with all applicable parties. We may be subject to claims that we or our employees, consultants or independent contractors have inadvertently or otherwise used or disclosed confidential information of our employees' former employers or other third parties. We may also be subject to claims that former employers or other third parties have an ownership interest in our patents. Litigation may be necessary to defend against these claims. There is no guarantee of success in defending these claims, and if we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable personnel or intellectual property rights, such as exclusive ownership of, or right to use, valuable intellectual property. Even if we are successful, litigation could result in substantial cost and be a distraction to our management and other employees.

In addition, while it is our policy to require our employees, contractors and other third parties who may be involved in the conception or development of intellectual property to execute agreements assigning such intellectual property to us, we may be unsuccessful in executing such an agreement with each party who, in fact, conceives or develops intellectual property that we regard as our own. The assignment of intellectual property rights under such agreements 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. Any of the foregoing could have a material adverse effect on our business, financial condition, results of operations, and prospects.

Our use of "open source" software could subject our proprietary software to general release and subject us to possible litigation.

Our bioinformatics platform incorporates software licensed under so-called "open source" licenses and we may incorporate open source software into other technologies in the future. Usage of open source software can lead to greater risks than the use of other third-party commercial software, as open source licensors generally do not provide warranties or controls on origin of the software or other contractual protections or code quality, as it is generally freely accessible and made available to the general public on an "as-is" basis under the terms of a non-negotiable license. Some open source licenses contain requirements that the user disclose source code for modifications it makes to the open source software and license such modifications to third parties at no cost. We monitor our use of open source software in an effort to avoid uses in a manner that would require us to disclose or grant licenses under our proprietary source code based on our modifications of open source code. However, there can be no assurance that such efforts will be successful and we could face claims that we are utilizing open source software in breach of the applicable licenses, which could result in litigation that may cause us to be required to disclose our proprietary source code based on our modifications of open source code, incur expenses and be liable for damages and such litigation could distract our personnel from their normal responsibilities.

Risks Related to Our Employees, Managing Our Growth and Our Operations

Our future success depends on our ability to retain our key personnel and to attract, retain and motivate qualified personnel.

We are highly dependent on the development, regulatory, commercialization and business development expertise of Roni Mamluk, M.D., Ph.D., our Chief Executive Officer and President, as well as the other principal members of our management, scientific and clinical teams. Although we have formal employment agreements, offer letters or consulting agreements with our executive officers, these agreements do not prevent them from terminating their services at-will with 60 days' to three months' advance notice.

If we lose one or more of our executive officers or key employees, our ability to implement our business strategy successfully could be seriously harmed. 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 develop, gain regulatory approval of and commercialize product candidates successfully. Competition to hire from this limited pool is intense, and we may be unable to hire, train, retain or motivate these additional 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 be engaged by entities other than us and 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 highly qualified personnel, our ability to develop and commercialize product candidates will be limited.

We may engage in acquisitions or in-licensing transactions that could disrupt our business, cause dilution to our stockholders or reduce our financial resources.

In the future, we may enter into transactions to acquire or license, as applicable, other businesses, products or technologies. If we do identify suitable candidates, we may not be able to make such acquisitions or licenses on favorable terms, or at all. Any acquisitions or in-license we make may not strengthen our competitive position, and these transactions may be viewed negatively by customers or investors. We may decide to incur debt in connection with an acquisition or in-license or issue common stock or other equity securities to the stockholders of the counterparty, which would reduce the percentage ownership of our existing stockholders. We could incur losses resulting from undiscovered liabilities of the acquired business, product or technology that are not covered by the indemnification we may obtain from the seller. In addition, we may not be able to successfully integrate the acquired personnel, technologies and operations into our existing business in an effective, timely and non-disruptive manner. Acquisitions and in-licensing may also divert management attention from day-to-day responsibilities, increase our expenses and reduce our cash available for operations and other uses. We cannot predict the number, timing or size of future acquisitions or the effect that any such transactions might have on our operating results.

Our business and operations may suffer in the event of information technology system failures, cyberattacks or deficiencies in our cybersecurity.

In the ordinary course of our business, we collect and store sensitive data, including intellectual property, clinical trial data, proprietary business information, personal data and personally identifiable information of our clinical trial subjects and employees, in our data centers and on our networks. The secure processing, maintenance and transmission of this information is critical to our operations. Our information technology systems, as well as those of our CROs, other contractors and consultants, and other third parties that we interact with, are vulnerable to attack, damage or interruption from computer viruses, malware (e.g. ransomware), malicious code, hacking, cyberattacks, phishing attacks and other social engineering schemes, theft, natural disasters (including hurricanes), terrorism, war, power disruptions, telecommunication and electrical failures, human error, fraud, denial or degradation of service attacks, sophisticated nation-state and nation-state-supported actors, unauthorized access or use by persons inside our organization or persons with access to systems inside our organization or other events or disruptions. Attacks upon information technology systems are increasing in their frequency, levels of persistence, sophistication and intensity, and are being conducted by sophisticated and organized groups and individuals with a wide range of motives and expertise. As a result of the COVID-19 pandemic and the current conflict between Russia and Ukraine, we and third parties who we interact with may also face increased cybersecurity risks due to increase reliance on internet technology and the number of our employees who are working remotely, which may create additional opportunities for cybercriminals to exploit vulnerabilities. Furthermore, because the techniques used to obtain unauthorized access to, or to sabotage, systems change frequently and often are not recognized until launched against a target, we, our CROs, other contractors and consultants, and other third parties that we interact with may be unable to anticipate these techniques or implement adequate preventative measures. We, our CROs, other contractors and consultants, and other third parties that we interact with may also experience security breaches that may remain undetected for an extended period. Even if identified, we may be unable to adequately investigate or remediate incidents or breaches due to attackers increasingly using tools and techniques that are designed to circumvent controls, to avoid detection, and to remove or obfuscate forensic evidence. System redundancy and other continuity measures may be ineffective or inadequate, and business continuity and disaster recovery planning may not be sufficient for all eventualities.

Although, to our knowledge, we have not experienced any such significant security breach to date, any such breach could compromise our networks and the information stored there could be accessed, publicly disclosed, lost or stolen. Any such access, disclosure or other loss of information could result in legal claims or proceedings, liability under laws that protect the privacy of personal information, significant regulatory penalties, and such an event could disrupt our operations, damage our reputation, and cause a loss of confidence in us and our ability to conduct clinical trials, which could adversely affect our reputation and delay our clinical development of our product candidates. If such an event were to occur and cause interruptions in our operations or the operations of our CROs, other contractors and consultants, it could result in a material disruption of our development programs. For example, the loss of preclinical or clinical trial data from completed, ongoing or planned 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 were to result in a loss of or damage to our data or applications, or inappropriate disclosure of personal, confidential or proprietary information, we could incur liability and the further development of AL101, AL102 or any other product candidate could be delayed.

Risks Related to Our Common Stock

An active trading market for our common stock may not be sustained.

If an active trading market for our common stock is not sustained, you may not be able to sell your shares quickly or at the market price or at all. Our ability to raise capital to continue to fund operations by selling shares of our common stock and our ability to acquire other companies or technologies by using shares of our common stock as consideration may also be impaired.

The market price of our common stock may be volatile and fluctuate substantially, which could result in substantial losses for purchasers of our common stock.

Our stock price may be volatile. The stock market in general and the market for smaller biopharmaceutical companies in particular have experienced extreme volatility that has often been unrelated to the operating performance of particular companies. As a result of this volatility, you may not be able to sell your common stock at or above the price which you paid for it. The market price for our common stock may be influenced by many factors, including:

- any delay in the enrollment and completion of our clinical trials;
- inability to obtain additional funding;
- the success of competitive products or technologies;
- actual or expected changes in our growth rate relative to our competitors;
- results of clinical trials of our product candidates or those of our competitors;
- developments related to our existing or any future collaborations;
- adverse regulatory decisions;
- regulatory actions with respect to our product candidates or our competitors' products and product candidates;
- regulatory or legal developments in the United States and other countries;
- development of new product candidates that may address our markets and make our product candidates less attractive;
- changes in physician, hospital or healthcare provider practices that may make our product candidates less useful;
- inability to obtain adequate product supply for AL101, AL102 or any other product candidate, or the inability to do so at acceptable prices;
- developments or disputes concerning patent applications, issued patents or other proprietary rights;
- the recruitment or departure of key scientific or management personnel;
- the level of expenses related to any of our product candidates or clinical development programs;
- failure to meet or exceed financial estimates and projections of the investment community or that we provide to the public;
- the results of our efforts to discover, develop, acquire or in-license additional product candidates or products;
- actual or expected changes in estimates as to financial results, development timelines or recommendations by securities analysts;
- 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;
- market conditions in the pharmaceutical and biotechnology sectors;
- announcements of significant acquisitions, strategic collaborations, joint ventures or capital commitments by us or our competitors;
- significant lawsuits, including patent or shareholder litigation, and disputes or other developments relating to our proprietary rights, including patents, litigation matters and our ability to obtain patent protection for our technologies;
- trading volume of our common stock;
- short selling activities;
- general economic, industry and market conditions; and
- the other factors described in this "Risk Factors" section and elsewhere in this Annual Report on Form 10-K.

In addition, the trading prices for common stock of other biopharmaceutical companies have been highly volatile as a result of the COVID-19 pandemic and the current conflict between Russia and Ukraine. These situations continue to rapidly evolve. The extent to which they may impact our business, preclinical studies and clinical trials will depend on future developments, which are highly uncertain and cannot be predicted with confidence.

In the past, securities class action litigation has often been brought against a company following a decline in the market price of its securities. This risk is especially relevant for us because biopharmaceutical companies have experienced significant stock price volatility in recent years. If we face such litigation, it could result in substantial costs and a diversion of management's attention and resources, which could harm our business.

Our executive officers, directors and principal stockholders, if they choose to act together, have the ability to control or significantly influence all matters submitted to stockholders for approval.

Based on the number of shares of common stock outstanding as of December 31, 2021, our executive officers, directors and stockholders who own more than 5% of our outstanding common stock and their respective affiliates, in the aggregate, hold shares representing approximately 78% of our outstanding voting stock. As a result, if these stockholders choose to act together, they would be able to control or significantly influence all matters submitted to our stockholders for approval, as well as our management and affairs. For example, these persons, if they choose to act together, would control or significantly influence the election of directors, the composition of our management and approval of any merger, consolidation or sale of all or substantially all of our assets.

A significant portion of our total outstanding shares are eligible to be sold into the market in the near future, which could cause the market price of our common stock to drop significantly, even if our business is doing well.

Sales of a substantial number of shares of our common stock in the public market, or the perception in the market that the holders of a large number of shares intend to sell shares, could reduce the market price of our common stock. There were 14,080,383 shares of common stock outstanding as of December 31, 2021. Of those shares 9,005,411 shares were previously restricted as a result of securities laws or lock-up agreements, but are now eligible to be sold, unless held by one of our affiliates, in which case the resale of those securities are subject to volume limitations under Rule 144 of the Securities Act of 1933, as amended, or Rule 144. Moreover, certain holders of our common stock have rights, subject to specified conditions, to require us to file registration statements covering their shares or to include their shares in registration statements that we may file for ourselves or other stockholders, until such shares can otherwise be sold without restriction under Rule 144 or until the rights terminate pursuant to the terms of the investors' rights agreement between us and such holders. Pursuant to the 2021 Purchase Agreement (as defined herein), we agreed to use reasonable best efforts to register 2,249,998 shares issued, or issuable upon exercise of warrants issued, in the Private Placement (as defined herein), on a registration statement on Form S-3 promptly following the date such form is available for use by us, but in no event later than June 15, 2021. On June 6, 2021, we registered 2,249,998 shares, of which 333,333 shares were issued and outstanding and 1,916,665 shares were issuable upon exercise of warrants to purchase shares of common stock, on a registration statement on Form S-3 (File No. 333-256793). We have also registered all shares of common stock that issued under our equity compensation plans. Such shares can be freely sold in the public market upon issuance, subject to volume limitations applicable to affiliates.

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," as defined in the Jumpstart Our Business Startups Act of 2012, or the JOBS Act, and may remain an emerging growth company until the last day of the fiscal year following the fifth anniversary of the closing of our initial public offering. However, if certain events occur prior to the end of such five-year period, including if we become a "large accelerated filer," our annual gross revenues exceed $1.07 billion or we issue more than $1.0 billion of non-convertible debt in any three-year period, we will cease to be an emerging growth company prior to the end of such five-year period. For so long as we remain an emerging growth company, we are permitted and intend to rely on exemptions from certain disclosure requirements that are applicable to other public companies that are not emerging growth companies. These exemptions include:

- 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 in this Annual Report on Form 10-K;
- 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
- exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and shareholder approval of any golden parachute payments not previously approved.

We have taken advantage of reduced reporting burdens in this Annual Report on Form 10-K. In particular, in this Annual Report on Form 10-K, we have provided only two years of audited financial statements and have not included all of the executive compensation related information that would be required if we were not an emerging growth company. We cannot predict whether investors will find our common stock less attractive because we 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 stock and our stock price may be reduced or become more volatile. In addition, the JOBS Act provides that an emerging growth company can take advantage of an extended transition period for complying with new or revised accounting standards. This allows an emerging growth company to delay the adoption of these accounting standards until they would otherwise apply to private companies. We have elected to take advantage of this extended transition period.

If securities or industry analysts do not publish research or reports about our business, or if they issue an adverse, inaccurate or misleading opinion regarding our business, our stock price and trading volume may be negatively impacted.

The trading market for our common stock will be influenced by the research and reports that industry or securities analysts publish about us or our business. In the event any of the analysts who cover us issue an adverse, inaccurate or misleading opinion regarding us, our business model, our intellectual property or our stock performance, or if our target operating results fail to meet the expectations of analysts, our stock price would likely decline. If one or more of these analysts ceases coverage of us or fails to publish reports on us regularly, we could lose visibility in the financial markets, which in turn could cause our stock price or trading volume to decline.

We are a "smaller reporting company" and the reduced disclosure requirements applicable to smaller reporting companies may make our common stock less attractive to investors.

We are considered a "smaller reporting company." We are therefore entitled to rely on certain reduced disclosure requirements, such as an exemption from providing selected financial data and executive compensation information. We are also exempt from the requirement to obtain an external audit on the effectiveness of internal control over financial reporting provided in Section 404(b) of the Sarbanes-Oxley Act. These exemptions and reduced disclosures in our SEC filings due to our status as a smaller reporting company mean our auditors do not review our internal control over financial reporting and may make it harder for investors to analyze our results of operations and financial prospects. We cannot predict if investors will find our common stock less attractive because we may rely on these exemptions. If some investors find our common stock less attractive as a result, there may be a less active trading market for our common stock and our stock prices may be more volatile.

Provisions in our restated certificate of incorporation and restated bylaws and under Delaware law could make an acquisition of our company, 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 restated certificate of incorporation and our restated bylaws may discourage, delay or prevent a merger, acquisition or other change in control of our company that stockholders may consider favorable, including transactions in which you might otherwise receive a premium for your shares. These provisions could also 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 include those establishing:

- a classified board of directors with three-year staggered terms, which may delay the ability of stockholders to change the membership of a majority of our board of directors;
- no cumulative voting in the election of directors, which limits the ability of minority stockholders to elect director candidates;
- the exclusive right of our board of directors to elect a director to fill a vacancy created by the expansion of the board of directors or the resignation, death or removal of a director, which prevents stockholders from filling vacancies on our board of directors;
- the ability of our board of directors to authorize the issuance of shares of preferred stock and to determine the terms of those shares, including preferences and voting rights, without stockholder approval, which could be used to significantly dilute the ownership of a hostile acquirer;
- the ability of our board of directors to alter our bylaws without obtaining stockholder approval;
- the required approval of the holders of at least two-thirds of the shares entitled to vote at an election of directors to adopt, amend or repeal our bylaws or repeal the provisions of our restated certificate of incorporation regarding the election and removal of directors;
- a prohibition on stockholder action by written consent, which forces stockholder action to be taken at an annual or special meeting of our stockholders;

- the requirement that a special meeting of stockholders may be called only by the chairman of the board of directors, the chief executive officer, the president or the board of directors, which may delay the ability of our stockholders to force consideration of a proposal or to take action, including the removal of directors; and

- advance notice procedures that stockholders must comply with in order to nominate candidates to our board of directors or to propose matters to be acted upon at a stockholders' meeting, which may discourage or deter a potential acquirer from conducting a solicitation of proxies to elect the acquirer's own slate of directors or otherwise attempting to obtain control of us.

Moreover, because we are incorporated in Delaware, we are governed by the provisions of Section 203 of the General Corporation Law of the State of Delaware, 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. Furthermore, our restated certificate of incorporation specifies that, unless we consent in writing to the selection of an alternative forum, the Court of Chancery of the State of Delaware will be the sole and exclusive forum for most legal actions involving claims brought against us by stockholders. Any person or entity purchasing or otherwise acquiring any interest in shares of our capital stock shall be deemed to have notice of and to have consented to the provisions of our restated certificate of incorporation described above.

We believe this provision benefits us by providing increased consistency in the application of Delaware law by chancellors particularly experienced in resolving corporate disputes, efficient administration of cases on a more expedited schedule relative to other forums and protection against the burdens of multi-forum litigation. However, the provision may have the effect of discouraging lawsuits against our directors, officers, employees and agents as it may limit any stockholder's ability to bring a claim in a judicial forum that such stockholder finds favorable for disputes with us or our directors, officers, employees or agents. The enforceability of similar choice of forum provisions in other companies' certificates of incorporation has been challenged in legal proceedings, and it is possible that, in connection with any applicable action brought against us, a court could find the choice of forum provisions contained in our restated certificate of incorporation to be inapplicable or unenforceable in such action. If a court were to find the choice of forum provision contained in our restated certificate of incorporation to be inapplicable or unenforceable in an action, we may incur additional costs associated with resolving such action in other jurisdictions, which could adversely affect our business, financial condition or results of operations.

Our restated certificate of incorporation designates specific courts as the exclusive forum for certain litigation that may be initiated by our stockholders, which could limit our stockholders' ability to obtain a favorable judicial forum for disputes with us.

Our restated certificate of incorporation specifies that, unless we consent in writing to the selection of an alternative forum, the Court of Chancery of the State of Delaware will be the sole and exclusive forum for most legal actions involving claims brought against us by stockholders; provided that, the exclusive forum provision will not apply to suits brought to enforce any liability or duty created by the Securities Act, the Exchange Act, the rules and regulations thereunder or any other claim for which the federal courts have exclusive jurisdiction; and provided further that, if and only if the Court of Chancery of the State of Delaware dismisses any such action for lack of subject matter jurisdiction, such action may be brought in another state or federal court sitting in the State of Delaware. Our restated certificate of incorporation further provides that, unless we consent in writing to the selection of an alternative forum, the federal district courts of the United States of America shall, to the fullest extent permitted by law, be the sole and exclusive forum for the resolution of any complaint asserting a cause of action arising under the Securities Act. Any person or entity purchasing or otherwise acquiring any interest in shares of our capital stock shall be deemed to have notice of and to have consented to the provisions of our restated certificate of incorporation described above.

We believe these provisions benefit us by providing increased consistency in the application of Delaware law by chancellors particularly experienced in resolving corporate disputes and in the application of the Securities Act by federal judges, as applicable, efficient administration of cases on a more expedited schedule relative to other forums and protection against the burdens of multi-forum litigation. However, the provision may have the effect of discouraging lawsuits against our directors, officers, employees and agents as it may limit any stockholder's ability to bring a claim in a judicial forum that such stockholder finds favorable for disputes with us or our directors, officers, employees or agents. The enforceability of similar choice of forum provisions in other companies' certificates of incorporation has been challenged in legal proceedings, and it is possible that, in connection with any applicable action brought against us, a court could find the choice of forum provisions contained in our restated certificate of incorporation to be inapplicable or unenforceable in such action. If a court were to find the choice of forum provision contained in our restated certificate of incorporation to be inapplicable or unenforceable in an action, we may incur additional costs associated with resolving such action in other jurisdictions, which could adversely affect our business, financial condition or results of operations.

It may be difficult to enforce a U.S. judgment against us, our officers and directors named in this Annual Report on Form 10-K in Israel or the United States, or to assert U.S. securities laws claims in Israel or serve process on our officers and directors.

Not all of our directors or officers are residents of the United States and most of their and our assets are located outside the United States. Service of process upon our non-U.S. resident directors and officers may be difficult to obtain within the United States. We have been informed by our legal counsel in Israel that it may be difficult to assert claims under U.S. securities laws in original actions instituted in Israel or obtain a judgment based on the civil liability provisions of U.S. federal securities laws. Israeli courts may refuse to hear a claim based on a violation of U.S. securities laws against us or our non-U.S. officers and directors because Israel may not be the most appropriate forum to bring such a claim. In addition, even if an Israeli court agrees to hear a claim, it may determine that Israeli law and not U.S. law is applicable to the claim. If U.S. law is found to be applicable, the content of applicable U.S. law must be proved as a fact, which can be a time-consuming and costly process. Certain matters of procedure will also be governed by Israeli law. There is little binding case law in Israel addressing the matters described above. Additionally, Israeli courts might not enforce judgments obtained in the United States against us or our non-U.S. directors and executive officers, which may make it difficult to collect on judgments rendered against us or our non-U.S. officers and directors.

Moreover, an Israeli court will not enforce a non-Israeli judgment if it was given in a state whose laws do not provide for the enforcement of judgments of Israeli courts (subject to exceptional cases), if its enforcement is likely to prejudice the sovereignty or security of the State of Israel, if it was obtained by fraud or in the absence of due process, if it is at variance with another valid judgment that was given in the same matter between the same parties, or if a suit in the same matter between the same parties was pending before a court or tribunal in Israel at the time the foreign action was brought.

Risks Related to Our Operations in Israel

Political, economic and military instability in Israel may impede our ability to operate and harm our financial results.

Our principal executive offices and research and development facilities are located in Israel. Accordingly, political, economic and military conditions in Israel and the surrounding region could directly affect our business. Since the establishment of the State of Israel in 1948, a number of armed conflicts have occurred between Israel and its Arab neighbors, Hamas (an Islamist militia and political group in the Gaza Strip) and Hezbollah (an Islamist militia and political group in Lebanon). Any hostilities involving Israel or the interruption or curtailment of trade between Israel and its present trading partners could adversely affect our operations. Ongoing and revived hostilities or other Israeli political or economic factors, could prevent or delay shipments of our products, harm our operations and product development and cause any future sales to decrease. In the event that hostilities disrupt the ongoing operation of our facilities or the airports and seaports on which we depend to import and export our supplies and products, our operations may be materially adverse affected. Furthermore, in the past, the State of Israel and Israeli companies have been subjected to economic boycotts. Several countries, principally those in the Middle East, still restrict business with Israel and Israeli companies, and additional countries may impose restrictions on doing business with Israel and Israeli companies if hostilities in Israel or political instability in the region continues or increases. These restrictive laws and policies may seriously limit our ability to sell our products in these countries and may have an adverse impact on our operating results, financial conditions or the expansion of our business.

In addition, political uprisings and conflicts in various countries in the Middle East are affecting the political stability of those countries. This instability has raised concerns regarding security in the region and the potential for armed conflict. In Syria, a country bordering Israel, a civil war is taking place. In addition, there are concerns that Iran, which has previously threatened to attack Israel, may step up its efforts to achieve nuclear capability. Iran is also believed to have a strong influence among extremist groups in the region, such as Hamas in Gaza and Hezbollah in Lebanon, as well as a growing presence in Syria. Additionally, the Islamic State of Iraq and Levant, or ISIL, a violent jihadist group whose stated purpose is to take control of the Middle East, remains active in areas within close proximity to Israeli borders. The tension between Israel and Iran and/or these groups may escalate in the future and turn violent, which could affect the Israeli economy in general and us in particular. Any potential future conflict could also include missile strikes against parts of Israel, including our offices and facilities. Such instability may lead to deterioration in the political and trade relationships that exist between the State of Israel and certain other countries. Any armed conflicts, terrorist activities or political instability in the region could adversely affect business conditions, could harm our results of operations and could make it more difficult for us to raise capital. Parties with whom we do business may be disinclined to travel to Israel during periods of heightened unrest or tension, forcing us to make alternative arrangements when necessary in order to meet our business partners face to face. In addition, the political and security situation in Israel may result in parties with whom we have agreements involving performance in Israel claiming that they are not obligated to perform their commitments under those agreements pursuant to force majeure provisions in such agreements.

Our insurance does not cover losses that may occur as a result of an event associated with the security situation in the Middle East or for any resulting disruption in our operations. Although the Israeli government has in the past covered the reinstatement value of direct damages that were caused by terrorist attacks or acts of war, we cannot be assured that this government coverage will be maintained or, if maintained, will be sufficient to compensate us fully for damages incurred and the government may cease providing such coverage or the coverage might not suffice to cover potential damages. Any losses or damages incurred by us could have a material adverse effect on our business. Any armed conflicts, political instability, terrorism, cyberattacks or any other hostilities involving or threatening Israel would likely negatively affect business conditions generally and could harm our results of operations.

Our operations may be disrupted by the obligations of our personnel to perform military service.

Some of our employees in Israel are obligated to perform up to 36 days, and in some cases longer periods, of military reserve duty annually until they reach the age of 40 (or older, for citizens who hold certain positions in the Israeli armed forces reserves) and, in the event of a military conflict or emergency situations, could be called to immediate active duty for extended periods of time. In response to increases in terrorist activity, there have been periods of significant call-ups of military reservists. It is possible that there will be similar large-scale military reserve duty call-ups in the future. Our operations could be disrupted by the absence due to military service of a significant number of our employees or of one or more of our key employees for extended periods of time, and such disruption could materially adversely affect our business. Additionally, the absence of a significant number of the employees of our Israeli suppliers and subcontractors related to military service or the absence for extended periods of one or more of their key employees for military service may disrupt their operations which may subsequently disrupt our operations.

We may become subject to claims for remuneration or royalties for assigned service invention rights by our employees, which could result in litigation and adversely affect our business.

We have entered into assignment of invention agreements with our employees pursuant to which such individuals agree to assign to us all rights to any inventions created during their employment or engagement with us. A significant portion of our intellectual property has been developed by our employees in the course of their employment with us. Under the Israeli Patent Law, 1967, or the Patent Law, inventions conceived by an employee during the scope of his or her employment with a company and as a result thereof are regarded as "service inventions," which belong to the employer, absent a specific agreement between the employee and employer giving the employee service invention rights. The Patent Law also provides that if there is no agreement between an employer and an employee with respect to the employee's right to receive compensation for such "service inventions," the Israeli Compensation and Royalties Committee, or the Committee, a body constituted under the Patent Law, shall determine whether the employee is entitled to remuneration for his or her service inventions and the scope and conditions for such remuneration. The Committee will examine, on a case-by-case basis, the general contractual framework between the parties, using interpretation rules of the general Israeli contract laws. Further, the Committee has not yet determined one specific formula for calculating this remuneration (but rather uses the criteria specified in the Patent Law). Although our employees have agreed to assign to us service invention rights, as a result of uncertainty under Israeli law with respect to the efficacy of waivers of service invention rights, we may face claims demanding remuneration in consideration for assigned inventions. As a consequence of such claims, we could be required to pay additional remuneration or royalties to our current and/or former employees, or be forced to litigate such claims, which could negatively affect our business.

Our operations may be affected by negative economic conditions or labor unrest in Israel.

General strikes or work stoppages, including at Israeli ports, have occurred periodically or have been threatened in the past by Israeli trade unions due to labor disputes. These general strikes or work stoppages may have an adverse effect on the Israeli economy and on our business, including our ability to receive raw materials from our suppliers in a timely manner and could have a material adverse effect on our results of operations.

General Risks

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

We may also rely on trademarks and trade names to protect our business. If our trademarks and trade names are not adequately protected, we may not be able to build name recognition in our markets of interest and our business may be adversely affected. We may not be able to protect our rights to these trademarks and trade names, which we need to build name recognition among potential partners or customers in our markets of interest. At times, competitors may adopt trade names or trademarks similar to ours, thereby impeding our ability to build brand identity and possibly leading to market confusion. In addition, there could be potential trade name or trademark infringement claims brought by owners of other registered trademarks or trademarks that incorporate variations of our unregistered trademarks or trade names. Over the long term, if we are unable to successfully register our trademarks and trade names and establish name recognition based on our trademarks and trade names, then we may not be able to compete effectively and our business may be adversely affected. Our efforts to enforce or protect our proprietary rights related to trademarks, trade secrets, domain names, copyrights or other intellectual property may be ineffective and could result in substantial costs and diversion of resources and could adversely impact our financial condition or results of operations.

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

As a public company, and particularly after we are no longer an emerging growth company, we will incur significant legal, accounting and other expenses that we did not incur as a private company. The Sarbanes-Oxley Act of 2002, the Dodd-Frank Wall Street Reform and Consumer Protection Act, the listing requirements of The Nasdaq Global Market and other applicable securities rules and regulations impose various requirements on public companies, including establishment and maintenance of effective disclosure and financial controls and corporate governance practices. Our management and other personnel will need to devote a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations will increase our legal and financial compliance costs and will 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, which in turn could make it more difficult for us to attract and retain qualified members of our board of directors.

We are evaluating these rules and regulations, and cannot predict or estimate the amount of additional costs we may incur or the timing of such costs. These rules and regulations are often subject to varying interpretations, in many cases due to their lack of specificity, and, as a result, their application in practice may evolve over time as new guidance is provided by regulatory and governing bodies. This could result in continuing uncertainty regarding compliance matters and higher costs necessitated by ongoing revisions to disclosure and governance practices.

Pursuant to Section 404 of the Sarbanes-Oxley Act of 2002, or Section 404, we are required to furnish a report by our management on our internal control over financial reporting. However, while we remain an emerging growth company, 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 remain in compliance with Section 404, we need 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, 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 whether such 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 in certain periods we will not be able to conclude, within the prescribed time frame or at all, that our internal control over financial reporting is effective as required by Section 404. Additionally, if we identify one or more material weaknesses, it could result in an adverse reaction in the financial markets due to a loss of confidence in the reliability of our financial statements.

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

We have never declared or paid any cash dividends on our common stock. We currently anticipate that we will retain future earnings for the development, operation and expansion of our business and do not anticipate declaring or paying any cash dividends for the foreseeable future. As a result, capital appreciation, if any, of our common stock would be your sole source of gain on an investment in our common stock for the foreseeable future. See “Dividends” under Part II Item 5. “Market for Registrant’s Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities.”

We could be subject to securities class action litigation.

In the past, securities class action litigation has often been brought against a company following a decline in the market price of its securities. This risk is especially relevant for us because biopharmaceutical companies have experienced significant stock price volatility in recent years. If we face such litigation, it could result in substantial costs and a diversion of management’s attention and resources, which could harm our business.

We could be subject to changes in tax laws or their interpretation or additional taxes in or out of the United States, or could otherwise have exposure to additional tax liabilities.

We are subject to tax laws in each jurisdiction where we do business. Changes in tax laws or their interpretation could decrease the amount of revenues we receive, the value of any tax loss carry-forwards and tax credits recorded on our balance sheet and the amount of our cash flow, and adversely affect our business, financial condition or results of operations. In addition, other factors or events, including business combinations and investment transactions, changes in the valuation of our deferred tax assets and liabilities, adjustments to taxes upon finalization of various tax returns or as a result of deficiencies asserted by taxing authorities, increases in expenses not deductible for tax purposes, changes in available tax credits, changes in transfer pricing methodologies, other changes in the apportionment of our income and other activities among tax jurisdictions, and changes in tax rates, could also increase our future effective tax rate.

Our tax filings are subject to review or audit by the U.S. Internal Revenue Service (the "IRS") and state, local and non-U.S. taxing authorities. We exercise significant judgment in determining our worldwide provision for taxes and, in the ordinary course of our business, there may be transactions and calculations where the proper tax treatment is uncertain. We may also be liable for taxes in connection with businesses we acquire. Our determinations are not binding on the IRS or any other taxing authorities, and accordingly the final determination in an audit or other proceeding may be materially different than the treatment reflected in our tax provisions, accruals and returns. An assessment of additional taxes because of an audit could have a material adverse effect on our business, financial condition, results of operations and cash flows.

New income, sales, use or other tax laws, statutes, rules, regulations or ordinances could be enacted at any time, or interpreted, changed, modified or applied adversely to us, any of which could adversely affect our business operations and financial performance. For example, the United States government may enact significant changes to the taxation of business entities including, among others, a permanent increase in the corporate income tax rate, an increase in the tax rate applicable to the global intangible low-taxed income and elimination of certain exemptions, and the imposition of minimum taxes or surtaxes on certain types of income. In particular, in connection with the 2022 U.S. federal budget reconciliation, U.S. Congressional committees have proposed changes to tax law that could result in additional federal income taxes being imposed on us. We are currently unable to predict whether such changes will occur and, if so, the ultimate impact on our business. To the extent that such changes have a negative impact on us, our suppliers or our customers, including as a result of related uncertainty, these changes may materially and adversely impact our business, financial condition, results of operations and cash flows.

Item 1B. Unresolved Staff Comments.

None.

Item 2. Properties.

Our principal office is located at Oppenheimer 4, Rehovot 7670104, Israel, where we lease office and laboratory space under a lease agreement that terminates in 2029. We believe that our facilities are sufficient to meet our current needs and that suitable additional space will be available as and when needed.

Item 3. Legal Proceedings.

We are not subject to any material legal proceedings.

Item 4. Mine Safety Disclosures.

Not applicable.

INFORMATION ABOUT OUR EXECUTIVE OFFICERS AND DIRECTORS

The following table sets forth information regarding our executive officers and directors as of the date of this Annual Report on Form 10-K.

Name	Age	Position
Executive Officers		
Roni Mamluk, Ph.D.	54	Chief Executive Officer, President and Director
Yossi Maimon, CPA, M.B.A.	51	Chief Financial Officer
Gary Gordon, M.D., Ph.D.	69	Chief Medical Officer
Directors		
David Sidransky, M.D.	61	Chairman of the Board of Directors
Murray A. Goldberg	77	Director
Robert Spiegel, M.D., F.A.C.P.	72	Director
Vered Bisker-Leib, Ph.D., M.B.A.	51	Director

Executive Officers

Roni Mamluk, Ph.D. has served as our Chief Executive Officer and President and a member of our board of directors since November 2017. Prior to joining us, Dr. Mamluk held various management positions at Chiasma, Inc., a biopharmaceutical company, including as Chief Executive Officer from April 2013 to March 2015 and has served as a member of its board of directors since June 2017. Prior to her time at Chiasma, Dr. Mamluk was the head of preclinical development of an oncology product at Adnexus Therapeutics Inc., a biopharmaceutical company, from April 2004 to June 2006.

Dr. Mamluk received a B.Sc. in Animal Sciences from Hebrew University of Jerusalem and a Ph.D. in Biology of Reproduction from the Hebrew University of Jerusalem, where she graduated summa cum laude. Dr. Mamluk also held a postdoctoral fellowship in angiogenesis at Harvard Medical School. We believe that Dr. Mamluk's extensive scientific knowledge, experience with our company and experience serving on a public company board of directors qualifies her to serve on our board of directors.

Yossi Maimon, CPA, M.B.A. has served as our Chief Financial Officer since March 2019. Prior to joining us, Mr. Maimon served as Chief Financial Officer at Protalix BioTherapeutics Inc., a biopharmaceutical company, from October 2006 to July 2019. Prior to his time at Protalix, Mr. Maimon served as Chief Financial Officer of ColBar LifeScience Ltd., a medical device company, from 2002 to 2006. Mr. Maimon received a B.A. in Accounting from the City University of New York and an M.B.A. from Tel Aviv University. Mr. Maimon is licensed as a Certified Public Accountant in New York and Israel.

Gary Gordon, M.D., Ph.D. has served as our Chief Medical Officer since August 2019. Prior to joining us, Dr. Gordon served as Vice President of Oncology Development at AbbVie Inc., a biopharmaceutical company, from January 2013 to April 2018. Prior to his time at AbbVie, Dr. Gordon served as Divisional Vice President of Global Oncology Development at Abbott Laboratories, a medical device company, from April 2003 to December 2012. Prior to his time at Abbott, Dr. Gordon served as Chief Scientific Officer and Vice President of Clinical Affairs at Ovation Pharmaceuticals Inc., a biopharmaceutical company, from May 2001 to April 2003. Dr. Gordon received a B.S. in Biochemistry from the State University of New York at Stony Brook and a Ph.D. in Pharmacology and an M.D. from Johns Hopkins University School of Medicine.

Non-Employee Directors

David Sidransky, M.D. has served as the chairman of our board of directors since November 2017. Since July 1994, Dr. Sidransky has been the Director of the Head and Neck Cancer Research Division at Johns Hopkins University School of Medicine's Department of Otolaryngology and Professor of Oncology, Cellular & Molecular Medicine, Urology, Genetics, and Pathology at the John Hopkins University School of Medicine. Dr. Sidransky currently serves on the board of directors of Galmed Pharmaceuticals Ltd., a biopharmaceutical company, Orgenesis Inc., a pharmaceutical manufacturing company and Champions Oncology, Inc., a biopharmaceutical company, and is the chairman of the board of directors of Advaxis, Inc., a biotechnology company. He also serves on the board of directors of Biond Biologics Ltd., a private biotechnology company. Previously, Dr. Sidransky served on the board of directors of Akari Therapeutics plc, a biopharmaceutical company, and Rosetta Genomics Ltd., a molecular diagnostics company. In addition, Dr. Sidransky served as Director of the American Association for Cancer Research (AACR) from 2005 to 2008. Dr. Sidransky received a B.S. in Chemistry from Brandeis University and an M.D. from Baylor College of Medicine where he also completed his residency in Internal Medicine. We believe that Dr. Sidransky's pioneering academic work, extensive medical and scientific knowledge and experience serving on public company boards of directors qualify him to serve on our board of directors.

Murray A. Goldberg has served as a member of our board of directors since December 2017. Mr. Goldberg held various management positions at Regeneron Pharmaceuticals, Inc., a biopharmaceutical company, from March 1995 to March 2015, including as Senior Vice President of Administration and Assistant Secretary from October 2013 to March 2015, as Chief Financial Officer and Senior Vice President, Finance and Administration and Assistant Secretary from March 1995 to October 2013 and as Treasurer from March 1995 to October 2012. Mr. Goldberg previously served on the boards of directors of Aerie Pharmaceuticals Inc., a biopharmaceutical company, from August 2013 to June 2020, where he also served as the chairman of its audit committee, and Teva Pharmaceuticals Industries Ltd. from July 2017 to June 2020. Mr. Goldberg received a B.S. in Engineering from New York University, a Master's degree in International Economics from the London School of Economics and an M.B.A. from the University of Chicago. We believe that Mr. Goldberg is qualified to serve on our board of directors because of his broad financial, operational and transactional experience in the industry.

Robert Spiegel, M.D., F.A.C.P. has served as a member of our board of directors since December 2017. Since 2012, Dr. Spiegel has served as an Associate Professor at the Weill Cornell Medical School. In addition, Dr. Spiegel has served as a Senior Advisor to Warburg Pincus, a private equity firm, and an Advisor to the Israel Biotech Fund, a venture investment fund since 2010 and 2016, respectively. Prior to these positions, Dr. Spiegel served as Chief Medical Officer of PTC Therapeutics, Inc., a biopharmaceutical company, from March 2011 to April 2016. Prior to his time at PTC Therapeutics, Dr. Spiegel held various management positions at Schering-Plough Corporation, a global healthcare company, including as Chief Medical Officer and Senior Vice President of the Schering-Plough Research Institute, the pharmaceutical research arm of the Schering-Plough Corporation from 1998 to 2009. Dr. Spiegel is currently a member of the board of directors of Geron Corporation and Cyclacel Pharmaceuticals, Inc., biopharmaceutical company, since 2010 and 2018, respectively. Dr. Spiegel has previously served as a member of the board of directors for Sucampo Pharmaceuticals, Inc., a biopharmaceutical company, Edge Therapeutics, Inc., a biotechnology company, Avior Computing Corporation, a privately-held governance risk and compliance process technology company, Talon Therapeutics, Inc., a biopharmaceutical company, Capstone Therapeutics Corp., a biotechnology company, the Cancer Institute of New Jersey and Cancer Care New Jersey. Dr. Spiegel received a B.A. in 1971 from Yale University and an M.D. from the University of Pennsylvania in 1975. Following his residency in internal medicine, Dr. Spiegel completed a fellowship in medical oncology at the National Cancer Institute. We believe that Dr. Spiegel's extensive medical and scientific knowledge as well as his experience in the life science industry qualifies him to serve on our board of directors.

Vered Bisker-Leib, Ph.D., M.B.A. has served as a member of our board of directors since August 2020. Dr. Bisker-Leib is the President and Chief Operating Officer of Compass Therapeutics, Inc. where she has been a member of the executive leadership team since November 2017. Prior to Compass, Dr. Bisker-Leib advised Atlas Ventures portfolio companies as an entrepreneur-in-residence from November 2016 to November 2017. Previously, as the Chief Business Officer of Cydan Development, Inc. from October 2014 to October 2016, Dr. Bisker-Leib founded biotech companies focused on therapies addressing rare diseases, including Imara Inc. Dr. Bisker-Leib was a member of Bristol-Myers Squibb's strategic transactions group where she assumed roles of increasing responsibility across five therapeutic areas, most recently as an Executive Director and Global Head of business development for the cardiovascular and metabolic franchises. Dr. Bisker-Leib received a Ph.D. in Chemical Engineering and an M.B.A. from the University of Massachusetts, Amherst. Dr. Bisker-Leib has a B.Sc. in Chemical Engineering from the Israel Institute of Technology, Haifa. We believe that Dr. Bisker-Leib's extensive experience in the life-science industry qualifies her to serve on our board of directors.

PART II

Item 5. Market for Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities.

Market Information and Holders

Our common stock is traded on The Nasdaq Global Market under the symbol "AYLA." On March 1, 2022, there were 22 holders of record of our common stock.

Dividends

We have never declared or paid any cash dividends on our capital stock. We currently intend to retain all available funds and future earnings, if any, for the operation and expansion of our business and do not anticipate declaring or paying any dividends in the foreseeable future. The payment of dividends, if any, will be at the discretion of our board of directors and will depend on our results of operations, capital requirements, financial condition, prospects, contractual arrangements, any limitations on payment of dividends present in our future debt agreements, and other factors that our board of directors may deem relevant.

Purchases of Equity Securities by the Issuer or Affiliated Purchasers

None.

Recent Sales of Unregistered Securities

None.

Use of Proceeds

On May 12, 2020, we completed our IPO and issued and sold 3,666,667 shares of our common stock at a price to the public of $15.00 per share. On June 9, 2020, in connection with the partial exercise of the underwriters' option to purchase additional shares, we issued and sold 274,022 additional shares of common stock at a price of $15.00 per share. The offer and sale of all of the shares in the offering was registered under the Securities Act pursuant to a Registration Statement on Form S-1 (File No. 333-236942), as amended, filed in connection with our IPO, or the Registration Statement, which was declared effective by the SEC on May 7, 2020. The offering terminated after the sale of all securities registered pursuant to the Registration Statement. The net proceeds have been invested in short- and intermediate-term investments in accordance with our investment policy. These investments may include money market funds and investment securities consisting of U.S. Treasury notes, and high quality, marketable debt instruments of corporations and government sponsored enterprises. There has been no material change in the expected use of the net proceeds from our IPO as described in the final prospectus (File
No. 333-236942) filed with the SEC pursuant to Rule 424(b)(4) under the Securities Act on May 11, 2020 in connection with our IPO, or the Final Prospectus.

Item 6. [Reserved].

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

You should read the following discussion and analysis of our financial condition and results of operations together with our consolidated financial statements and the related notes included elsewhere in this Annual Report on Form 10-K. Some of the information contained in this discussion and analysis or set forth elsewhere in this Annual Report on Form 10-K, including information with respect to our plans and strategy for our business and related financing, includes forward-looking statements that involve risks and uncertainties. As a result of many factors, including those factors set forth in the "Risk Factors" section of this Annual Report on Form 10-K, our actual results could differ materially from the results described in or implied by the forward-looking statements contained in the following discussion and analysis. A discussion of the year ended December 31, 2020 compared to the year ended December 31, 2019 has been reported previously in our Annual Report on Form 10-K for the year ended December 31, 2020, filed with the SEC on March 24, 2021, under the heading "Management's Discussion and Analysis of Financial Condition and Results of Operations."

Overview

We are a clinical-stage oncology company focused on developing and commercializing small molecule therapeutics for patients suffering from rare and aggressive cancers, primarily in genetically defined patient populations. Our differentiated development approach is predicated on identifying and addressing tumorigenic drivers of cancer, through a combination of our bioinformatics platform and next-generation sequencing to deliver targeted therapies to underserved patient populations. Our current portfolio of product candidates, AL101 and AL102, targets the aberrant activation of the Notch pathway using gamma secretase inhibitors. Gamma secretase is the enzyme responsible for Notch activation and, when inhibited, turns off the Notch pathway activation. Aberrant activation of the Notch pathway has long been implicated in multiple solid tumor and hematological cancers and has often been associated with more aggressive cancers. In cancers, Notch is known to serve as a critical facilitator in processes such as cellular proliferation, survival, migration, invasion, drug resistance and metastatic spread, all of which contribute to a poorer patient prognosis. AL101 and AL102 are designed to address the underlying key drivers of tumor growth, and our initial Phase 2 clinical data of AL101 suggest that our approach may address shortcomings of existing treatment options. We believe that our novel product candidates, if approved, have the potential to transform treatment outcomes for patients suffering from rare and aggressive cancers.

Our product candidates, AL101 and AL102, are being developed as potent, selective, small molecule gamma secretase inhibitors, or GSIs. We obtained an exclusive, worldwide license to develop and commercialize AL101 and AL102 from Bristol-Myers Squibb Company, or BMS, in November 2017. BMS evaluated AL101 in three Phase 1 studies involving more than 200 total subjects and AL102 in a single Phase 1 study involving 36 subjects with various cancers who had not been prospectively characterized for Notch activation, and to whom we refer to as unselected subjects. While these Phase 1 studies did not report statistically significant overall results, clinical activity was observed across these studies in cancers in which Notch has been implicated as a tumorigenic driver.

We are currently evaluating AL102, our oral GSI for the treatment of desmoid tumors, in a Phase 2/3 pivotal study. Initial interim data read-out from Part A and dose selection is expected around mid-2022 with Part B of the study to commence immediately thereafter. Part B of the study will be a double-blind placebo-controlled study enrolling up to 156 patients with progressive disease, randomized between AL102 or placebo. The study's primary endpoint will be progression free survival, or PFS with secondary endpoints including ORR, duration of response, or DOR and patient reported QOL measures.

In addition, we are collaborating with Novartis International Pharmaceutical Limited, or Novartis, to develop AL102 for the treatment of multiple myeloma, or MM, in combination with Novartis' B-cell maturation antigen, or BCMA, targeting therapies. The first patient was dosed with AL102 in combination with Novartis' BCMA targeting agent in April 2021.

We are currently evaluating AL101 as a monotherapy in an open-label Phase 2 clinical trial for the treatment of recurrent/metastatic adenoid cystic carcinoma, or R/M ACC, for patients bearing Notch-activating mutations. We refer to this trial as the ACCURACY trial. We use next-generation sequencing, or NGS, to identify patients with Notch-activating mutations, an approach that we believe will enable us to target the patient population with cancers that we believe are most likely to respond to and benefit from AL101 treatment. We chose to initially target R/M ACC based on our differentiated approach, which is comprised of: data generated in a Phase 1 study of AL101 in unselected, heavily pretreated subjects conducted by BMS, our own data generated in patient-derived xenograft models, our bioinformatics platform and our expertise in the Notch pathway.

We are currently conducting our ongoing Phase 2 ACCURACY trial for the treatment of recurrent/metastatic adenoid cystic carcinoma, or R/M ACC, in subjects with progressive disease and Notch-activating mutations. If approved, we believe that AL101 has the potential to be the first therapy approved by the FDA for patients with R/M ACC and address the unmet medical need of these patients. AL101 was granted Orphan Drug Designation in May 2019 for the treatment of adenoid cystic carcinoma, or ACC, and fast track designation in February 2020 for the treatment of R/M ACC. In the second quarter of 2020, we commenced dosing of patients in our ACCURACY trial for the treatment of R/M ACC with Notch-activating mutations at the higher dose of 6mg. We reported initial data from this trial in 2021 and plan to report additional data in 2022.

We are also developing AL102 for the treatment of T-ALL, an aggressive, rare form of T-cell specific leukemia. Based on findings from our Phase 1 study of AL101 and supporting data from our preclinical studies, we intend to commence a Phase 2 clinical trial of AL102 for the treatment of R/R T-ALL in the second half of 2022, subject to the impact of COVID-19 on our business.

As part of our efforts to focus our resources on the more advanced programs and studies including the RINGSIDE study in desmoid tumors and the ACCURACY study for ACC, we elected to discontinue the TENACITY trial, which was evaluating AL101 as a monotherapy in an open-label Phase 2 clinical trial for the treatment of patients with Notch-activated R/M TNBC.

We were incorporated as a Delaware corporation on November 14, 2017, and our headquarters is located in Rehovot, Israel. Our operations to date have been limited to organizing and staffing our company, business planning, raising capital and conducting research and development activities for our product candidates. To date, we have funded our operations primarily through the sales of common stock and convertible preferred stock.

We have incurred significant net operating losses in every year since our inception and expect to continue to incur significant expenses and increasing operating losses for the foreseeable future. Our net losses may fluctuate significantly from quarter to quarter and year to year and could be substantial. Our net losses were $40.3 million and $30.1 million for the years ended December 31, 2021 and 2020, respectively. As of December 31, 2021, we had an accumulated deficit of $111.1 million. We anticipate that our expenses will increase significantly as we:

- advance our development of AL101 for the treatment of R/M ACC;
- advance our Phase 2/3 RINGSIDE pivotal trial of AL102 for the treatment of desmoid tumors, or obtain and conduct clinical trials for any other product candidates;
- assuming successful completion of our Phase 2 ACCURACY trial of AL101 for the treatment of R/M ACC, may be required by the FDA to complete Phase 3 clinical trials to support submission of a New Drug Application, or NDA, of AL101 for the treatment of R/M ACC;
- establish a sales, marketing and distribution infrastructure to commercialize AL101 and/or AL102, if approved, and for any other product candidates for which we may obtain marketing approval;
- collaborate with leading diagnostic companies to develop diagnostic tests for identifying patients with Notch-activating mutations;
- maintain, expand, protect and enforce our intellectual property portfolio;
- hire additional staff, including clinical, scientific, technical, regulatory operational, financial, commercial and other personnel, to execute our business plan; and
- add clinical, scientific, operational, financial and management information systems and personnel to support our product development and potential future commercialization efforts, and to enable us to operate as a public company.

We do not expect to generate revenue from product sales unless and until we successfully complete clinical development and obtain regulatory approval for a product candidate. Additionally, we currently use contract research organizations, or CROs, to carry out our clinical development activities. Furthermore, we incur additional costs associated with operating as a public company. As a result, we will need substantial additional funding to support our continuing operations, pursue our growth strategy and continue as a going concern. Until such time as we can generate significant revenue from product sales, if ever, we expect to fund our operations through public or equity offerings or debt financings, marketing and distribution arrangements and other collaborations, strategic alliances and licensing arrangements or other sources. We may, however, be unable to raise additional funds or enter into such other arrangements when needed on favorable terms or at all. Our failure to raise capital or enter into such other arrangements as and when needed would have a negative impact on our financial condition and our ability to develop our current or any future product candidates.

Because of the numerous risks and uncertainties associated with therapeutics product development, we are unable to predict accurately the timing or amount of increased expenses or when or if we will be able to achieve or maintain profitability. Even if we are able to generate revenue from product sales, we may not become profitable. If we fail to become profitable or are unable to sustain profitability on a continuing basis, then we may be unable to continue our operations at planned levels and be forced to reduce or terminate our operations.

As of December 31, 2021, we had cash and cash equivalents and restricted cash totaling $37.3 million. Due to the uncertainty in securing additional funding, and the insufficient amount of cash and cash equivalent resources at December 31, 2021, we have concluded that substantial doubt exists with respect to our ability to continue as a going concern within one year after the date of the filing of this Annual Report on Form 10-K. See "—Liquidity and Capital Resources." Substantial doubt about our ability to continue as a going concern may materially and adversely affect the price per share of our common stock, and it may be more difficult for us to obtain financing. If potential collaborators decline to do business with us or potential investors decline to participate in any future financings due to such concerns, our ability to increase our cash position may be limited. We will need to generate significant revenues to achieve profitability, and we may never do so. Because of the numerous risks and uncertainties associated with the development of our current and any future product candidates, the development of our platform and technology and because the extent to which we may enter into collaborations with third parties for development of any of our product candidates is unknown, we are unable to estimate the amounts of increased capital outlays and operating expenses required for completing the research and development of our product candidates.

If we raise additional funds through marketing and distribution arrangements and other collaborations, strategic alliances and licensing arrangements with third parties, we may be required to relinquish valuable rights to our technologies, intellectual property, future revenue streams or product candidates or grant licenses on terms that may not be favorable to us. If we are unable to raise additional funds through equity or debt financings when needed, we may be required to delay, limit, reduce or terminate product candidate development programs or future commercialization efforts, grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves or discontinue operations.

License Agreements

Bristol-Myers Squibb

In November 2017, we entered into an exclusive worldwide license agreement with Bristol-Myers Squibb Company, or BMS, for AL101 and AL102, each a small molecule gamma secretase inhibitor in development for the treatment of cancers. Under the terms of the license agreement, we have licensed the exclusive worldwide development and commercialization rights for AL101 (previously known as BMS-906024) and AL102 (previously known as BMS-986115).

We are responsible for all future development and commercialization of AL101 and AL102. In consideration for the rights granted under the agreement, we paid BMS a payment of $6 million and issued to BMS 1,125,929 shares of Series A preferred stock valued at approximately $7.3 million. We are obligated to pay BMS up to approximately $142 million in the aggregate upon the achievement of certain clinical development or regulatory milestones and up to $50 million in the aggregate upon the achievement of certain commercial milestones by each product containing the licensed BMS compounds. In addition, we are obligated to pay BMS tiered royalties ranging from a high single-digit to a low teen percentage on worldwide net sales of all products containing the licensed BMS compounds.

BMS has the right to terminate the BMS License Agreement in its entirety upon written notice to us (a) for insolvency-related events involving us, (b) for our material breach of the BMS License Agreement if such breach remains uncured for a defined period of time, (c) for our failure to fulfill our obligations to develop or commercialize the BMS Licensed Compounds and/or BMS Licensed Products not remedied within a defined period of time following written notice by BMS, or (d) if we or our affiliates commence any action challenging the validity, scope, enforceability or patentability of any of the licensed patent rights. We have the right to terminate the BMS License Agreement (a) for convenience upon prior written notice to BMS, the length of notice dependent on whether a BMS Licensed Product has received regulatory approval, (b) upon immediate written notice to BMS for insolvency-related events involving BMS, (c) for BMS's material breach of the BMS License Agreement if such breach remains uncured for a defined period of time, or (d) on a BMS Licensed Compound-by-BMS Licensed Compound and/or BMS Licensed Product-by-BMS Licensed Product basis upon immediate written notice to BMS if we reasonably determine that there are unexpected safety and public health issues relating to the applicable BMS Licensed Compounds and/or BMS Licensed Products. Upon termination of the BMS License Agreement in its entirety by us for convenience or by BMS, we grant an exclusive, non-transferable, sublicensable, worldwide license to BMS under certain of our patent rights that are necessary to develop, manufacture or commercialize BMS Licensed Compounds or BMS Licensed Products. In exchange for such license, BMS must pay us a low single-digit percentage royalty on net sales of the BMS Licensed Compounds and/or BMS Licensed Products by it or its affiliates, licensees or sublicensees, provided that the termination occurred after a specified developmental milestone for such BMS Licensed Compounds and/or BMS Licensed Products. For more information regarding this agreement, please see "Business—License Agreements."

Novartis

In December 2018, we entered into an evaluation, option and license agreement, or the Novartis Agreement, with Novartis International Pharmaceutical Limited, or Novartis, pursuant to which we granted Novartis an exclusive option to obtain an exclusive license to research, develop, commercialize and manufacture AL102 for the treatment of multiple myeloma.

We will continue to supply Novartis quantities of AL102, products containing AL102 and certain other materials for purposes of conducting evaluation studies not comprising human clinical trials during the option period, together with our know-how as may reasonably be necessary in order for Novartis to conduct such evaluation studies. Novartis has agreed to reimburse us for all such expenses.

At any time during the option term, Novartis may exercise its option by payment of a low eight figure option exercise fee. If Novartis exercises its option, it will be obligated to pay us up to an additional $245 million upon the achievement of certain clinical development and commercial milestones. In addition, Novartis is obligated to pay us tiered royalties at percentages ranging from a mid-single digit to a low double-digit percentage on worldwide net sales of products licensed under the agreement.

The option we granted to Novartis will remain in effect until the earlier of (a) 60 days following the last visit of the last subject in the evaluation studies, (b) the termination of the Novartis Agreement, or (c) 36 months following the delivery by us to Novartis of sufficient amounts of clinical evaluation materials to conduct the anticipated clinical studies. The Novartis Agreement remains in effect until such time as no Novartis Licensed Product is being developed or commercialized by Novartis, its affiliates, or sublicensees (including distributors or commercial partners), unless terminated earlier. We have the right to terminate the Novartis Agreement (a) for Novartis's material breach if such breach remains uncured for 60 days (such cure period shall be extended for an additional period during which Novartis is making good faith efforts to cure such breach) or (b) for Novartis's failure to use commercially reasonable efforts to develop or commercialize AL102 and/or the Novartis Licensed Product not remedied within four months following written notice to Novartis. Novartis has the right to terminate the Novartis Agreement (a) in its entirety or on a country-by-country basis for convenience, upon 60 days' written notice to us, (b) for our material breach if such breach remains uncured for 60 days (such cure period shall be extended for an additional period during which we are making good faith efforts to cure such breach) or (c) upon immediate written notice to us for insolvency-related events involving us. For more information regarding this agreement, please see "Business—License Agreements."

Components of Results of Operations

Revenue Recognition

We recognize revenue in accordance with ASC Topic 606, Revenue from Contracts with Customers, which applies to all contracts with customers. Under Topic 606, an entity recognizes revenue when its customer obtains control of promised goods or services, in an amount that reflects the consideration that the entity expects to receive in exchange for those goods or services. To determine revenue recognition for arrangements that an entity determines are within the scope of Topic 606, the entity performs the following five steps:

(i) identify the contract(s) with a customer;

(ii) identify the performance obligations in the contract;

(iii) determine the transaction price;

(iv) allocate the transaction price to the performance obligations in the contract; and

(v) recognize revenue when (or as) the entity satisfies a performance obligation.

At contract inception, once the contract is determined to be within the scope of Topic 606, we assess the goods or services promised within the contract and determine those that are performance obligations and assess whether each promised good or service is distinct.

Customer option to acquire additional goods or services gives rise to a performance obligation in the contract only if the option provides a material right to the customer that it would not receive without entering into that contract.

In a contract with multiple performance obligations, we must develop estimates and assumptions that require judgment to determine the underlying stand-alone selling price for each performance obligation, which determines how the transaction price is allocated among the performance obligations.

We evaluate each performance obligation to determine if it can be satisfied at a point in time or over time.

Revenue is recognized when control of the promised goods or services is transferred to the customers, in an amount that reflects the consideration we expect to be entitled to receive in exchange for those goods or services.

In December 2018, we entered into the Novartis Agreement for which we paid for its research and development costs. For additional details regarding the Novartis Agreement, refer to Note 5 of our consolidated financial statements included elsewhere in this Annual Report on Form 10-K.

We concluded that there is one distinct performance obligation under the Novartis Agreement: Research and development services, an obligation which is satisfied over time.

Revenue associated with the research and development services in the amount of $3.5 million was recognized in the year ended December 31, 2021, compared to $3.7 million in fiscal year 2020.

We concluded that progress towards completion of the research and development performance obligation related to the Novartis Agreement is best measured in an amount proportional to the expenses incurred from the total estimated expenses. We periodically review and update our estimates, when appropriate, which may adjust revenue recognized for the period. The transaction price to be recognized as revenue under the Novartis Agreement consists of the reimbursable research and development costs.

Operating Expenses

Our operating expenses since inception have consisted solely of research and development expenses and general and administrative expenses.

Research and Development Expenses

Research and development expenses consist primarily of costs incurred for our research activities, including the development of and pursuit of regulatory approval of our lead product candidates, AL101 and AL102, which include:

- employee-related expenses, including salaries, benefits and stock-based compensation expense for personnel engaged in research and development functions;
- expenses incurred in connection with the preclinical and clinical development of our product candidates, including under agreements with CROs, investigative sites and consultants;
- costs of manufacturing our product candidates for use in our preclinical studies and clinical trials, as well as manufacturers that provide components of our product candidates for use in our preclinical and current and potential future clinical trials;
- costs associated with our bioinformatics platform;
- consulting and professional fees related to research and development activities;
- costs related to compliance with clinical regulatory requirements; and
- facility costs and other allocated expenses, which include expenses for rent and maintenance of our facility, utilities, depreciation and other supplies.

We expense research and development costs as incurred. Our external research and development expenses consist primarily of costs such as fees paid to consultants, contractors and CROs in connection with our preclinical and clinical development activities. We typically use our employee and infrastructure resources across our development programs and we do not allocate personnel costs and other internal costs to specific product candidates or development programs with the exception of the costs to manufacture our product candidates.

The following table summarizes our research and development expenses by product candidate or development program for the years ended December 31, 2021 and 2020:

	Years Ended December 31,	
	2021	**2020**
Program-specific costs:		
AL101		
ACC	$ 15,363	$ 13,684
TNBC	8,051	6,828
General Expenses	1,484	1,563
AL102		
General Expenses	42	39
Desmoid	5,001	292
Total research and development expenses	$ 29,941	$ 22,406

Research and development activities are central to our business model. Product candidates in later stages of clinical development 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. We expect that our research and development expenses will continue to be significant for the foreseeable future as we continue to advance our pivotal Phase 2/3 RINGSIDE study of AL102 for the treatment of desmoid tumors and initiate additional clinical trials, including AL102 for the treatment of R/R T-ALL, scale our manufacturing processes, continue to develop additional product candidates and hire additional clinical and scientific personnel.

The successful development of AL101, AL102 and any future product candidate is highly uncertain. Accordingly, at this time, we cannot reasonably estimate or know the nature, timing and costs of the efforts that will be necessary to complete the development of these product candidates. We are also unable to predict when, if ever, we will generate revenue and material net cash inflows from the commercialization and sale of any of our product candidates for which we may obtain marketing approval. We may never succeed in achieving regulatory approval for any of our product candidates. The duration, costs and timing of preclinical studies, clinical trials and development of our product candidates will depend on a variety of factors, including:

- successful completion of clinical trials with adequate safety, tolerability and efficacy profiles for AL101, AL102 and any potential future product candidates that are satisfactory to the FDA or any comparable foreign regulatory authority;
- approval of INDs for AL101 and AL102 and any potential future product candidate to commence planned or future clinical trials in the United States or foreign countries;
- significant and changing government regulation and regulatory guidance;
- timing and receipt of marketing approvals from applicable regulatory authorities;
- establishing arrangements with contract manufacturing organizations, or CMOs, for third-party clinical and commercial manufacturing to obtain sufficient supply of our product candidates;
- obtaining, maintaining, protecting and enforcing patent and other intellectual property rights and regulatory exclusivity for our product candidates;
- commercializing the product candidates, if and when approved, whether alone or in collaboration with other organizations;
- acceptance of the product, if and when approved, by patients, the medical community and third-party payors;
- competition with other therapies; and
- maintenance of a continued acceptable safety profile of the products following approval.

A change in the outcome of any of these variables with respect to the development, manufacture or commercialization enabling activities of any of our product candidates would significantly change the costs, timing and viability associated with the development of that product candidate. For example, if the FDA or another regulatory authority were to require us to conduct clinical trials beyond those that we anticipate will be required for the completion of clinical development of a product candidate, or if we experience significant delays in our clinical trials due to patient enrollment or other reasons, we would be required to expend significant additional financial resources and time on the completion of clinical development.

General and Administrative Expenses

General and administrative expenses consist primarily of salaries and other related costs, including stock-based compensation, for personnel in executive, finance and administrative functions. General and administrative expenses also include direct and allocated facility-related costs as well as professional fees for legal, patent, consulting, investor and public relations, accounting, auditing, tax services and insurance costs.

We expect that our general and administrative expenses will increase in the future to support continued research and development activities and potential commercialization of our product candidates. These increases will likely include increased costs related to the hiring of additional personnel and fees to outside consultants, attorneys and accountants, among other expenses. Additionally, we expect to incur increased expenses associated with being a public company, including the costs of additional personnel, accounting, audit, legal, regulatory and tax-related services associated with maintaining compliance with exchange listing and Securities and Exchange Commission, or SEC, requirements, director and officer insurance costs, and investor and public relations costs.

Financial Income, Net

Financial income, net primarily consists of interest income earned on our cash and cash equivalents and restricted bank deposits.

Critical Accounting Policies and Use of Estimates

Our management's discussion and analysis of financial condition and results of operations is based on our consolidated financial statements, which have been prepared in accordance with accounting principles generally accepted in the United States, or GAAP. The preparation of these financial statements requires us to make estimates and judgments that affect the reported amounts of assets, liabilities and expenses and the disclosure of contingent assets and liabilities in our consolidated financial statements during the reporting periods. These items are monitored and analyzed by us for changes in facts and circumstances, and material changes in these estimates could occur in the future. We base our estimates on historical experience, known trends and events, and on various other factors that we believe are reasonable under the circumstances, the results of which form the basis for making judgments about the carrying value of assets and liabilities that are not readily apparent from other sources. Changes in estimates are reflected in reported results for the period in which they become known. Actual results may differ materially from these estimates under different assumptions or conditions.

While our significant accounting policies are described in more detail in the notes to our consolidated financial statements appearing elsewhere in this Annual Report on Form 10-K, we believe the following accounting policies used in the preparation of our consolidated financial statements require the most significant judgments and estimates.

Accrued Research and Development Expenses

As part of the process of preparing our consolidated financial statements, we are required to estimate our accrued research and development expenses. This process involves reviewing purchase orders and open contracts, communicating with our personnel to identify services that have been performed on our behalf and calculating the level of service performed and the associated cost incurred for the services when we have not yet been invoiced or otherwise notified of the actual cost. The majority of our service providers invoice us monthly in arrears for services performed, on a pre-determined schedule or when contractual milestones are met; however, some require advance payments. We make calculations of our accrued expenses as of each balance sheet date in our consolidated financial statements based on facts and circumstances known to us at that time. We periodically confirm the accuracy of our calculations with the service providers and make adjustments if necessary. The significant calculation in our accrued research and development expenses include the following costs incurred for services in connection with research and development activities for which we have not yet been invoiced:

- vendors in connection with clinical development activities;
- vendors in connection with the testing of clinical trial materials;
- CROs in connection with clinical trials; and
- investigative sites in connection with clinical trials.

We contract with CROs to conduct clinical and other research and development services on our behalf. We base our expenses related to CROs on our calculations of the services received and efforts expended pursuant to quotes and contracts with them. The financial terms of these agreements are subject to negotiation, vary from contract to contract and may result in uneven payment flows. There may be instances in which payments made to our CROs will exceed the level of services provided and result in a prepayment of the research and development 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 our estimate, we adjust the accrual or amount of prepaid expense accordingly. Non-refundable advance payments for goods and services that will be used in future research and development activities are expensed when the activity has been performed or when the goods have been received rather than when the payment is made.

Although we do not expect our calculations 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 calculations of accrued research and development expenses.

Stock-Based Compensation

We measure stock options and other stock-based awards granted to employees, directors, consultants or advisors of the company or its affiliates based on their fair value on the date of the grant and recognize compensation expense of those awards, over the requisite service period, which is generally the vesting period of the respective award. We apply the accelerated method of expense recognition to all awards with only service-based vesting conditions.

For stock-based awards granted to non-employees, compensation expense is recognized over the period during which services are rendered by such non-employees until completed.

We estimate the fair value of each stock option grant on the date of grant using the Black-Scholes option-pricing model, which uses as inputs the fair value of our common stock and assumptions we make for the volatility of our common stock, the expected term of our stock options, the risk-free interest rate for a period that approximates the expected term of our stock options and our expected dividend yield.

Previously, as a private company with no active public market for our common stock, our board of directors historically determined the fair value of our common stock on each date of grant, with input from management. Our board of directors periodically determined the estimated per share fair value of our common stock at various dates using valuations performed by third parties. All options to purchase shares of our common stock were intended to be granted with an exercise price per share no less than the fair value per share of our common stock underlying those options on the date of grant, based on the information known to us on the date of grant. Our determinations of the fair value of our common stock were made using methodologies, approaches and assumptions consistent with the American Institute of Certified Public Accountants Audit and Accounting Practice Aid Series: *Valuation of Privately Held Company Equity Securities Issued as Compensation*, or the Practice Guide.

Our board of directors considered various objective and subjective factors, along with input from management, to determine the fair value of our common stock, including:

- the lack of an active public market for our common stock and convertible preferred stock;
- the prices at which we sold shares of our convertible preferred stock in arm's-length transactions and the superior rights, preferences and privileges of the convertible preferred stock relative to our common stock, including the liquidation preferences of our preferred stock;
- our results of operations and financial condition, including cash on hand;
- the material risks related to our business;
- our stage of development and business strategy;
- the composition of, and changes to, our management team and board of directors;
- the market performance of publicly traded companies in the life sciences and biotechnology sectors, as well as recently completed initial public offerings, or IPOs, of companies in the life sciences and biotechnology sectors; and
- the likelihood of achieving a liquidity event such as an IPO given prevailing market conditions.

Our valuations were prepared in accordance with the guidelines in the Practice Guide, which prescribes several valuation approaches for setting the value of an enterprise, such as the cost, income and market approaches, and various methodologies for allocating the value of an enterprise to its common stock. Through September 2019, we utilized the option pricing method, or OPM, and a guideline transaction method, which we believed was the most appropriate for each of the valuations of our common stock performed by our independent third-party valuation specialist. The OPM treats our security classes as call options on total equity value, and allocates our equity value across its security classes based on the rights and preferences of the securities within the capital structure under an assumed liquidation event. The OPM method is used when the range of possible future outcomes is difficult to predict and forecasts would be highly speculative. We believed this method was the most appropriate given the expectation of various potential liquidity outcomes and the difficulty of selecting appropriate enterprise values given our early stage of development, while allowing us to accurately capture the potential downside risk of our clinical-stage assets. Beginning in November 2019, for options granted after September 30, 2019, we utilized a hybrid of the OPM and Probability-Weighted Expected Return Method, or PWERM. The PWERM is a scenario based analysis that estimates the value per share based on the probability-weighted present value of expected future investment returns, considering each of the possible outcomes available to us, as well as the economic and control rights of each share class. Under this hybrid method, we considered both the initial public offering liquidity scenario and an alternative scenario in the event an initial public offering does not occur. In October 2019, we engaged a new third-party valuation firm to retrospectively estimate the value of our common stock as of certain prior dates. Stock-based compensation was awarded as a result of such retrospective valuations.

There are significant judgments and estimates inherent in the determination of the fair value of our common stock. These judgments and estimates are management's best estimates and include assumptions regarding our future operating performance, the time to completing an initial public offering or other liquidity event, the related company valuations associated with such events and the determinations of the appropriate valuation methods. If we had made different assumptions, our stock-based compensation expense, net loss and net loss per common share could have been different.

Results of Operations

Comparison of the year ended December 31, 2021 and 2020

The following table summarizes our results of operations for the year ended December 31, 2021 and 2020 (in thousands):

	Years Ended December 31,		
	2021	2020	% Change
Revenue from license agreement	$ 3,506	$ 3,708	(5)%
Cost of revenue	(3,506)	(3,708)	(5)
Gross profit	—	—	—
Operating expenses:			
Research and development	29,941	22,406	34
General and administrative	9,277	7,371	26
Operating loss	(39,218)	(29,777)	32
Financial income (expense), net	(260)	56	(564)
Loss before income tax	(39,478)	(29,721)	33
Taxes on income	(776)	(425)	83
Net loss	$ (40,254)	$ (30,146)	34%

Revenue

Revenue associated with the research and development services under the Novartis Agreement in the amount of $3.5 million was recognized in the year ended December 31, 2021, compared to $3.7 million recognized in fiscal year 2020. For additional details regarding the Novartis Agreement, refer to Note 5 of our consolidated financial statements included elsewhere in this Annual Report on Form 10-K.

Research and Development Expenses

Research and development expenses were $29.9 million for the year ended December 31, 2021 compared to $22.4 million for the year ended December 31, 2020, an increase of $7.5 million. This increase was primarily driven by additional costs in connection with the initiation and advancement of the Phase 2/3 RINGSIDE pivotal study for desmoids tumors.

General and Administrative Expenses

General and administrative expenses were $9.3 million for the year ended December 31, 2021 compared to $7.4 million for the year ended December 31, 2020, an increase of $1.9 million. This increase was primarily due to higher expenses in connection with our operations as a public company, including officer and director insurance, increased headcount and stock-based compensation.

Financial Income (expense), net

Financial expense, net was $260 thousand for the year ended December 31, 2021 compared to financial income, net of $56 thousand for the year ended December 31, 2020.

Liquidity and Capital Resources

Sources of Liquidity

Since our inception, we have not generated any revenue from product sales and have incurred significant operating losses and negative cash flows from our operations. Our net losses were $40.3 million and $30.1 million for the year ended December 31, 2021 and 2020, respectively. As of December 31, 2021, we had an accumulated deficit of $111.1 million.

On May 12, 2020, we completed the sale of shares of our common stock in our IPO. In connection with the IPO, we issued and sold 3,940,689 shares of common stock, including 274,022 shares associated with the partial exercise on June 4, 2020 of the underwriters' option to purchase additional shares, at a price to the public of $15.00 per share, resulting in net proceeds to us of approximately $52.2 million after deducting underwriting discounts and commissions and estimated offering expenses payable by us. All shares issued and sold were registered pursuant to the Registration Statement.

On February 19, 2021, we entered into a Securities Purchase Agreement (the "2021 Purchase Agreement") with the purchasers named therein (the "Investors"). Pursuant to the 2021 Purchase Agreement, we agreed to sell (i) an aggregate of 333,333 shares of our common stock (the "Private Placement Shares"), par value $0.01 per share, together with warrants to purchase an aggregate of 116,666 shares of our common stock with an exercise price of $18.10 per share (the "Common Warrants"), for an aggregate purchase price of $4,999,995.00 and (ii) pre-funded warrants to purchase an aggregate of 1,333,333 shares of our common stock with an exercise price of $0.01 per share (the "Pre-Funded Warrants" and collectively with the Common Warrants, the "Private Placement Warrants"), together with an aggregate of 466,666 Common Warrants, for an aggregate purchase price of $19,986,661.67 (collectively, the "Private Placement"). The Private Placement closed on February 23, 2021.

In June 2021, we entered into an Open Market Sales Agreement, or the Sales Agreement, with Jefferies LLC, or Jefferies, as sales agent, pursuant to which we may, from time to time, issue and sell common stock with an aggregate value of up to $200.0 million in "at-the-market" offerings, under our Registration Statement on Form S-3 (File No. 333-256792) filed with the SEC on June 4, 2021 (the "ATM"). Sales of common stock, if any, pursuant to the Sales Agreement, may be made in sales deemed to be an "at the market offering" as defined in Rule 415(a) of the Securities Act, including sales made directly through The Nasdaq Global Market or on any other existing trading market for our common stock. Pursuant to the Sales Agreement, during the year ended December 31, 2021, we sold a total of 827,094 shares of common stock for total gross proceeds of approximately $10.4 million.

The exercise price and the number of shares of common stock issuable upon exercise of each Private Placement Warrant 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. In addition, in certain circumstances, upon a fundamental transaction, a holder of Common Warrants will be entitled to receive, upon exercise of the Common Warrants, the kind and amount of securities, cash or other property that such holder would have received had they exercised the Private Placement Warrants immediately prior to the fundamental transaction. The Pre-Funded Warrants will be automatically exercised on cashless basis upon the occurrence of a fundamental transaction. Each Common Warrant is exercisable from the date of issuance and has a term of three years and each Pre-Funded Warrant is exercisable from the date of issuance and has a term of ten years. Pursuant to the 2021 Purchase Agreement, we registered the Private Placement Shares and Private Placement Warrants for resale by the Investors on a registration statement on Form S-3.

The Private Placement was exempt from registration pursuant to Section 4(a)(2) of the Securities Act and Regulation D promulgated thereunder, as a transaction by an issuer not involving a public offering.

The following table provides information regarding our total cash and cash equivalents and restricted bank cash at December 31, 2021 and 2020 (in thousands):

	As of December 31,	
	2021	2020
Cash and cash equivalents and restricted cash	$ 37,339	$ 42,370

Cash Flows

The following table provides information regarding our cash flows for the years ended December 31, 2021 and 2020 (in thousands):

	Years Ended December 31,	
	2021	2020
Net cash used in operating activities	$ (38,356)	$ (27,541)
Net cash (used in) provided by investing activities	(5)	181
Net cash provided by financing activities	33,330	52,922
Net increase (decrease) in cash and cash equivalents and restricted cash	$ (5,031)	$ 25,562

Net Cash Used in Operating Activities

The cash used in operating activities resulted primarily from expenses associated with our clinical development programs and early-stage research and general and administrative expenses.

Net cash used in operating activities during the year ended December 31, 2021 of $38.4 million was primarily attributable to our net loss of $40.3 million, adjusted for stock-based compensation of $2.7 million.

Net cash used in operating activities during the year ended December 31, 2020 of $27.5 million was primarily attributable to our net loss of $30.1 million, adjusted for non-cash expenses of $2.6 million, which includes stock-based compensation of $1.6 million and a net decrease in working capital of $1.0 million.

Net Cash Used in Investing Activities

Net cash used in investing activities during the year ended December 31, 2021, of $5 thousand was attributable to purchases of property and equipment.

Net cash provided by investing activities during the year ended December 31, 2020, of $181 thousand was primarily attributable to maturing of bank deposits.

Net Cash Provided by Financing Activities

Net cash provided by financing activities during the year ended December 31, 2021 of 33.3 million was primarily attributable to our issuance of shares and warrants, net of issuance costs.

Net cash provided by financing activities during the year ended December 31, 2020 of $52.9 million was primarily attributable to our IPO, net of issuance costs.

Funding Requirements and Going Concern

We expect our expenses to continue to be significant in connection with our ongoing activities, particularly as we continue the research and development for, initiate later-stage clinical trials for, and seek marketing approval for, our product candidates. In addition, if we obtain marketing approval for any of our product candidates, we expect to incur significant commercialization expenses related to product sales, marketing, manufacturing and distribution. Furthermore, we incur additional costs associated with operating as a public company. Accordingly, we will need to obtain substantial additional funding in connection with our continuing operations. If we are unable to raise capital when needed or on attractive terms, we would be forced to delay, reduce or eliminate our research and development programs or future commercialization efforts.

As of December 31, 2021, we had cash and cash equivalents and restricted cash of $37.3 million. We evaluated whether there are conditions and events, considered in the aggregate, that raise substantial doubt about our ability to continue as a going concern within one year after the date that the audited consolidated financial statements are issued. Due to the uncertainty in securing additional funding, and the insufficient amount of cash and cash equivalent resources at December 31, 2021, we have concluded that substantial doubt exists with respect to our ability to continue as a going concern within one year after the date of the filing of this Annual Report on Form 10-K.

Our future capital requirements will depend on many factors, including:

- the costs of conducting future clinical trials of AL101 and AL102;
- the costs of manufacturing additional material for future clinical trials of AL101 and AL102;
- the scope, progress, results and costs of discovery, preclinical development, laboratory testing and clinical trials for other potential product candidates we may develop, if any;
- the costs, timing and outcome of regulatory review of our product candidates;
- the achievement of milestones or occurrence of other developments that trigger payments under any current or future license, collaboration, or other agreements;
- the costs and timing of future commercialization activities, including product sales, marketing, manufacturing and distribution, for any of our product candidates for which we receive marketing approval;
- the amount of revenue, if any, received from commercial sales of our product candidates, should any of our product candidates receive marketing approval;
- the costs of preparing, filing and prosecuting patent applications, obtaining, maintaining, protecting and enforcing our intellectual property rights and defending intellectual property-related claims;
- the severity, duration and impact of the COVID-19 pandemic, which may adversely impact our business and clinical trials;
- our headcount growth and associated costs as we expand our business operations and our research and development activities; and
- the costs of operating as a public company.

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 marketing 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 products that we do not expect to be commercially available for many years, if at all. Accordingly, we will need to continue to rely on additional financing to achieve our business objectives. Adequate additional financing may not be available to us on acceptable terms, or at all.

Until such time, if ever, as we can generate substantial product revenues, we expect to finance our cash needs through a combination of equity offerings, debt financings, collaborations, strategic alliances and licensing arrangements. 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 interests may be diluted, and the terms of these securities may include liquidation or other preferences that could adversely affect your rights as a common stockholder. Any debt financing, if available, may involve agreements that include restrictive covenants that limit our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends, that could adversely impact our ability to conduct our business.

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

Emerging Growth Company Status

The Jumpstart Our Business Startups Act of 2012, or the JOBS Act, 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. We have elected to use this extended transition period under the JOBS Act. As a result, our financial statements may not be comparable to the financial statements of issuers who are required to comply with the effective dates for new or revised accounting standards that are applicable to public companies, which may make comparison of our financials to those of other public companies more difficult.

We will remain an emerging growth company until the earliest to occur of: (1) the last day of the fiscal year (a) following the fifth anniversary of the completion of our IPO, or December 31, 2025, (b) in which we have total annual gross revenues of $1.07 billion or more, or (c) in which we are deemed to be a large accelerated filer under the rules of the SEC, which means the market value of our outstanding common stock held by non-affiliates exceeds $700 million as of last business day of our most recently completed second fiscal quarter, and (2) the date on which we have issued more than $1.0 billion in nonconvertible debt during the previous three years.

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

We are exposed to market risk related to changes in interest rates. As of December 31, 2020, and 2021, our cash equivalents consisted of interest-bearing checking accounts. Our primary exposure to market risk is interest rate sensitivity, which is affected by changes in the general level of U.S. interest rates. Due to the short-term nature and the low-risk profile of our interest-bearing accounts, an immediate 10% change in interest rates would not have a material effect on the fair market value of our cash and cash equivalents and short-term restricted bank deposits or on our financial position or results of operations. We are not currently exposed to significant market risk related to changes in foreign currency exchange rates; however, we have contracted with and may continue to contract with foreign vendors located in Europe and Israel. Our operations may be subject to fluctuations in foreign currency exchange rates in the future. Inflation generally affects us by increasing our clinical trial costs. We do not believe that inflation had a material effect on our business, financial condition or results of operations during the years ended December 31, 2020 or 2021.

Item 8. Financial Statements and Supplementary Data.

AYALA PHARMACEUTICALS, INC.
INDEX TO FINANCIAL STATEMENTS

Kost Forer Gabbay & Kasierer
144 Menachem Begin Road, Building A
Tel-Aviv 6492102, Israel

Tel: +972-3-6232525
Fax: +972-3-5622555
ey.com

Report of Independent Registered Public Accounting Firm
To the Shareholders and the Board of Directors of

AYALA PHARMACEUTICALS, INC.

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of Ayala Pharmaceuticals, Inc. (the Company) as of December 31, 2021 and 2020, and the related consolidated statements of operations, changes in stockholders' equity and cash flows for each of the two years in the period ended December 31, 2021 and the related notes (collectively referred to as the "consolidated financial statements"). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company at December 31, 2021 and 2020, and the results of its operations and its cash flows for each of the two years in the period ended December 31, 2021, in conformity with U.S. generally accepted accounting principles.

The Company's Ability to Continue as a Going Concern

The accompanying consolidated 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, has a negative cash flows from operating activities, 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 consolidated 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 misstatements, 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/ KOST FORER GABBAY & KASIERER

A Member of Ernst & Young Global

We have served as the Company's auditor since 2017.

Tel-Aviv, Israel

March 28, 2022

AYALA PHARMACEUTICALS, INC.

CONSOLIDATED BALANCE SHEETS

U.S. dollars in thousands (except share and per share data)

	December 31, 2021	December 31, 2020
Assets		
Current Assets:		
Cash and Cash Equivalents	$ 36,982	$ 42,025
Short-Term Restricted Bank Deposits	122	90
Trade Receivables	-	681
Prepaid Expenses and Other Current Assets	2,636	1,444
Total Current Assets	39,740	44,240
Long-Term Assets:		
Other Assets	267	305
Property and Equipment, Net	1,120	1,283
Total Long-Term Assets	1,387	1,588
Total Assets	$ 41,127	$ 45,828
Liabilities and Stockholders' Equity:		
Current Liabilities:		
Trade Payables	$ 3,214	$ 3,726
Other Accounts Payables	3,258	3,151
Total Current Liabilities	6,472	6,877
Long-Term Liabilities:		
Long-Term Rent Liability	497	553
Total Long-Term Liabilities	$ 497	$ 553
Stockholders' Equity:		
Common Stock of $0.01 par value per share; 200,000,000 shares authorized at December 31, 2021 and 2020; 14,080,383 and 12,824,463 shares issued at December 31, 2021 and 2020, respectively; 13,956,035 and 12,728,446 shares outstanding at December 31, 2021 and 2020, Respectively.	$ 139	$ 128
Additional Paid-in Capital	145,160	109,157
Accumulated Deficit	(111,141)	(70,887)
Total Stockholders' Equity	34,158	38,398
Total Liabilities and Stockholders' Equity	$ 41,127	$ 45,828

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

AYALA PHARMACEUTICALS, INC.

CONSOLIDATED STATEMENTS OF OPERATIONS

U.S. dollars in thousands (except shares and per shares data)

	Year ended December 31, 2021	Year ended December 31, 2020
Revenue from License Agreement	$ 3,506	$ 3,708
Cost of Revenue	(3,506)	(3,708)
Gross Profit	—	—
Research and Development	$ 29,941	$ 22,406
General and Administrative	9,277	7,371
Operating Loss	(39,218)	(29,777)
Financial income (expenses), net	(260)	56
Loss before taxes on income	(39,478)	(29,721)
Taxes on Income	(776)	(425)
Net Loss	$ (40,254)	$ (30,146)
Net Loss per Share attributable to Common Stockholders, Basic and Diluted	$ (2.80)	$ (3.06)
Weighted Average Shares Used to Compute Net Loss per Share, Basic and Diluted	14,398,905	9,860,610

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

AYALA PHARMACEUTICALS, INC.

STATEMENT OF CHANGES IN STOCKHOLDERS' EQUITY

U.S. dollars in thousands (except share amounts)

	Convertible Preferred Stock									
	Series A Preferred Stock		Series B Preferred Stock		Total	Common Stock		Additional paid-in	Accumulated	Total Stockholders' (Deficit)
	Number	Amount	Number	Amount	Amount	Number	Amount	capital	Deficit	Equity
Balance as of December 31, 2019	3,679,778	$ 23,823	3,750,674	$ 29,550	$ 53,373	4,998,874	$ 51	$ 1,770	$ (40,741)	$ (38,920)
Conversion of Preferred Stock into Common stock	(3,679,778)	(23,823)	(3,750,674)	(29,550)	(53,373)	3,715,222	37	53,336	—	53,373
Issuance of Common Stock, Initial Public Offering, net of Issuance Cost of $2,730	—	—	—	—	—	3,940,689	39	52,202	—	52,241
Exercise of Stock Option	—	—	—	—	—	54,999	1	280	—	281
Stock Based Compensation	—	—	—	—	—	18,662	*	1,569		1,569
Net Loss	—	—	—	—	—	—	—	—	(30,146)	(30,146)
Balance as of December 31, 2020	—	$ —	—	$ —	$ —	12,728,446	$ 128	$ 109,157	$ (70,887)	$ 38,398
Proceeds from Issuance of common stock and warrants, net of issuance cost of $1,724	—	—	—	—	—	333,333	3	23,259	—	23,262
Proceeds from Issuance of common stock net of issuance cost of $438	—	—	—	—	—	827,094	8	9,959	—	9,967
Exercise of Stock Options	—	—	—	—	—	18,328	*	101	—	101
Stock Based Compensation	—	—	—	—	—	48,834	*	2,684	—	2,684
Net Loss	—	—	—	—	—	—	—	—	(40,254)	(40,254)
Balance as of December 31, 2021	—	$ —	—	$ —	$ —	13,956,035	$ 139	$ 145,160	$ (111,141)	$ 34,158

* Represents an amount lower than $1.

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

AYALA PHARMACEUTICALS, INC.

STATEMENTS OF CONSOLIDATED CASH FLOWS

U.S. dollars in thousands

	Year Ended December 31, 2021	Year Ended December 31, 2020
Cash Flows from Operating Activities:		
Net Loss	$ (40,254)	$ (30,146)
Adjustments to reconcile Net Loss to Net Cash used in Operating Activities:		
Shared Based Compensation	2,684	1,569
Depreciation	168	182
Increase in Prepaid Expenses and other Assets	(1,174)	(1,029)
Decrease (Increase) in trade receivables	681	(212)
Increase in Trade Payables	(512)	451
Increase in other Accounts Payable	51	1,644
Net Cash used in Operating Activities	(38,356)	(27,541)
Cash Flows from Investing Activities:		
Proceeds from Maturities of Long-Term Deposits	—	226
Purchase of Property and Equipment	(5)	(45)
Net Cash provided by (used in) Investing Activities	(5)	181
Cash Flows from Financing Activities:		
Exercise of Stock Options	101	281
Issuance of shares and warrants, net	23,262	—
Proceeds from Issuance of Shares, net	9,967	52,641
Net Cash provided by Financing Activities	33,330	52,922
Increase (Decrease) in Cash and Cash Equivalents and Restricted Cash	(5,031)	25,562
Cash and Cash Equivalents and Restricted Cash at Beginning of the Year	42,370	16,808
Cash and Cash Equivalents and Restricted Cash at End of the Year	$ 37,339	$ 42,370
Supplemental Disclosure of Non-Cash Financing Activities		
Non-cash Deferred Offering Costs	$ -	$ 400
Supplemental Disclosures of Cash Flow Information:		
Cash Received for Interest	$ 12	$ 58
Cash Paid for Income Taxes	$ 209	$ 300
Cash Received for Income Taxes	$ 32	$ -

	Year Ended December 31, 2021	Year Ended December 31, 2020
Cash and Cash Equivalents	$ 36,982	$ 42,025
Restricted Cash	122	90
Restricted Cash in Other Assets	235	255
Cash and Cash Equivalents and Restricted Cash at End of the Year	$ 37,339	$ 42,370

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

1. General

a) Ayala Pharmaceuticals, Inc. (the "Company") was incorporated in November 2017. The Company is a clinical stage oncology company dedicated to developing and commercializing small molecule therapeutics for patients suffering from rare and aggressive cancers, primarily in genetically defined patient populations. The Company's current portfolio of product candidates, AL101 and AL102, target the aberrant activation of the Notch pathway with gamma secretase inhibitors.

b) In 2017, the Company entered into an exclusive worldwide license agreement with respect to AL101 and AL102. See note 5.

c) The Company's lead product candidates, AL101 and AL102, have completed preclinical and Phase 1 studies. AL102 is currently being evaluated in a pivotal Phase 2/3 trial (RINGSIDE) in patients with Desmoids tumors and is being evaluated in a Phase 1 clinical trial in combination with Novartis' BMCA targeting agent, WVT078, in Patients with relapsed/refractory Multiple Myeloma. AL101 is currently being evaluated in a Phase 2 trial (ACCURACY) in patients with recurrent/metastatic adenoid cystic carcinoma ("R/M ACC") bearing Notch-activating mutations is ongoing.

d) The Company has a wholly-owned Israeli subsidiary, Ayala-Oncology Israel Ltd. (the "Subsidiary"), which was incorporated in November 2017.

Initial Public Offering and Other Transactions

On May 12, 2020, the Company completed the sale of shares of its common stock in its IPO. In connection with the IPO, the Company issued and sold 3,940,689 shares of its common stock, par value $0.01 per share ("Common Stock") including 274,022 shares associated with the partial exercise on June 4, 2020 of the underwriters' option to purchase additional shares, at a price to the public of $15.00 per share, resulting in net proceeds to the Company of approximately $52.2 million after deducting underwriting discounts and commissions and offering expenses payable by the Company. All shares issued and sold were registered pursuant to a registration statement on Form S-1 (File No. 333-236942), as amended, declared effective by the U.S. Securities and Exchange Commission (the "Commission") on May 7, 2020.

In connection with the IPO, the Company effected a one-for-two reverse stock split of its Common Stock which became effective on May 4, 2020. Upon the closing of the IPO, all of the outstanding shares of Series A preferred stock and Series B preferred stock automatically converted into an aggregate of 3,715,222 shares of Common Stock. Subsequent to the closing of the IPO, there were no preferred shares outstanding.

On February 19, 2021, the Company entered into a Securities Purchase Agreement (the "2021 Purchase Agreement") with the purchasers named therein (the "Investors"). Pursuant to the 2021 Purchase Agreement, the company agreed to sell (i) an aggregate of 333,333 shares of our common stock (the "Private Placement Shares"), par value $0.01 per share, together with warrants to purchase an aggregate of 116,666 shares of its Common Stock with an exercise price of $18.10 per share (the "Common Warrants"), for an aggregate purchase price of $4,999,995.00 and (ii) pre-funded warrants to purchase an aggregate of 1,333,333 shares of its Common Stock with an exercise price of $0.01 per share (the "Pre-Funded Warrants" and collectively with the Common Warrants, the "Private Placement Warrants"), together with an aggregate of 466,666 Common Warrants, for an aggregate purchase price of $19,986,661.67 (collectively, the "Private Placement"). The Private Placement closed on February 23, 2021.

In June 2021, the Company entered into an Open Market Sales Agreement, or the Sales Agreement, with Jefferies LLC, or Jefferies, as sales agent, pursuant to which the Company may, from time to time, issue and sell Common Stock with an aggregate value of up to $200.0 million in "at-the-market" offerings, under its Registration Statement on Form S-3 (File No. 333-256792) filed with the SEC on June 4, 2021 (the "ATM"). Sales of Common Stock, if any, pursuant to the Sales Agreement, may be made in sales deemed to be an "at the market offering" as defined in Rule 415(a) of the Securities Act, including sales made directly through The Nasdaq Global Market or on any other existing trading market for its Common Stock. Pursuant to the Sales Agreement, during the year ended December 31, 2021, the Company sold a total of 827,094 shares of Common Stock for total gross proceeds of approximately $10.4 million.

Going Concern

The Company has incurred recurring losses since inception as a research and development organization and has an accumulated deficit of $111.1 million as of December 31, 2021. For the year ended December 31, 2021, the Company used $38.4 million of cash in operations. The Company has relied on its ability to fund its operations through public and private equity financings. The Company expects operating losses and negative cash flows to continue at significant levels in the future as it continues its clinical trials. As of December 31, 2021, the Company had approximately $37.3 million in cash and cash equivalents and restricted cash, which, without additional funding, the Company believes will not be sufficient to meet its obligations within the next twelve months from the date of issuance of these consolidated financial statements. The Company plans to continue to fund its operations through public or private debt and equity financings, but there can be no assurances that such financing will continue to be available to the Company on satisfactory terms, or at all. If the Company is unable to obtain funding, the Company would be forced to delay, reduce or eliminate its research and development programs, which could adversely affect its business prospects, or the Company may be unable to continue operations. As such, those factors raise substantial doubt about the Company's ability to continue as a going concern.

The consolidated financial statements have been prepared assuming that the Company will continue as a going concern. Therefore, the consolidated financial statements for the year ended December 31, 2021 do not include any adjustments to reflect the possible future effects on the recoverability and classification of assets or the amounts and classification of liabilities that may result from uncertainty related to the Company's ability to continue as a going concern.

2. Significant Accounting Policies

The consolidated financial statements have been prepared in accordance with U.S. generally accepted accounting principles ("U.S. GAAP"). The significant accounting policies followed in the preparation of the consolidated financial statements, are as follows:

Use of Estimates:

The preparation of financial statements in conformity with U.S. GAAP requires management to make estimates, judgments and assumptions that affect the amounts reported in the consolidated financial statements and accompanying notes. The Company's management believes that the estimates, judgment and assumptions used are reasonable based upon information available at the time they are made. These estimates, judgments and assumptions can affect the reported amounts of assets and liabilities and disclosure of contingent assets and liabilities at the dates of the consolidated financial statements. Actual results could differ from those estimates.

Consolidated Financial Statements in U.S. Dollars

A substantial portion of the Company's financing activities, including equity transactions and cash investments, are incurred in U.S. dollars. The Company's management believes that the U.S. dollar is the currency of the primary economic environment in which the Company operates. Thus, the functional and reporting currency of the Company is the U.S. dollar.

A subsidiary's functional currency is the currency of the primary economic environment in which the subsidiary operates; normally, that is the currency of the environment in which a subsidiary primarily generates and expends cash. In making the determination of the appropriate functional currency for a subsidiary, the Company considers cash flow indicators, local market indicators, financing indicators and the subsidiary's relationship with both the parent company and other subsidiaries. For subsidiaries that are primarily a direct and integral component or extension of the parent entity's operations, the U.S. dollar is the functional currency.

The Company has determined the functional currency of its foreign subsidiary is the U.S. Dollar. The foreign operation is considered a direct and integral part or extension of the Company's operations. The day-to-day operations of the foreign subsidiary are dependent on the economic environment of the U.S. Dollar.

Accordingly, monetary accounts maintained in currencies other than the U.S. dollar are remeasured into U.S. dollars in accordance with Statement of the Accounting Standard Codification ("ASC") No. 830 "Foreign Currency Matters" ("ASC No. 830"). All transaction gains and losses of the remeasured monetary balance sheet items are reflected in the statements of operations as financial income or expenses as appropriate.

Principles of Consolidation

The consolidated financial statements include the accounts of the Company and the Subsidiary. Intercompany balances and transactions have been eliminated upon consolidation.

Cash and Cash Equivalents and Short-term restricted bank deposits

The Company considers all highly liquid certificates of deposits with original maturities of three months or less from the purchase date to be cash equivalents. Cash equivalents consist primarily of amounts invested in money market accounts in the United States and are stated at fair value. Short-term restricted bank deposits consist of a bank deposit accounts that serves as collateral for a credit card agreement and lease agreements at one of the Company's financial institutions.

Property and Equipment, Net

Property and equipment are stated at cost, less accumulated depreciation. Depreciation is calculated on a straight-line basis over the estimated useful lives of the related assets, at the following annual rates:

Computers and Software	33%
Lab Equipment	15%
Office Furniture and Equipment	7%

Leasehold improvements are amortized on a straight-line basis over the shorter of the assets' estimated useful life or the remaining term of the lease.

Maintenance and repair costs are expensed as incurred.

Impairment of Long-Lived Assets

The Company's long-lived assets are reviewed for impairment in accordance with ASC No. 360, "Property, Plant and Equipment," whenever events or changes in circumstances indicate that the carrying amount of an asset may not be recoverable. If indicators of impairment exist and the undiscounted future cash flows that the assets are expected to generate are less than the carrying value of the assets, the Company reduces the carrying amount of the assets through an impairment charge, to their estimated fair values. During the years ended December 31, 2021, and 2020, no impairment indicators have been identified.

Accrued Post-Employment Benefit

Under Israeli employment laws, employees of the Company are included under Section 14 of the Severance Compensation Act, 1963 ("Section 14") for a portion of their salaries. According to Section 14, these employees are entitled to monthly payments made by the Company on their behalf with insurance companies.

Payments in accordance with Section 14 release the Company from any future severance payments with respect to those employees. The obligation to make the monthly deposits is expensed as incurred. In addition, the aforementioned deposits are not recorded as an asset in the consolidated balance sheet, and there is no liability recorded as the Company does not have a future obligation to make any additional payments. Severance costs amounted to approximately $0.3 million and $0.2 million for the year ended December 31, 2021 and 2020, respectively.

The Company maintains a 401(k) retirement savings plan for its U.S. employees. Each eligible employee may elect to contribute a portion of the employee's compensation to the plan. As of December 31, 2021, and 2020, the Company has matched 100% of all employee contributions, up to 6% of the employee's base salary.

Fair Value of Financial Instruments:

The Company measures and discloses the fair value of financial assets and liabilities in accordance with ASC Topic 820, "Fair Value Measurement." Fair value is based on the price that would be received to sell an asset or paid to transfer a liability in an orderly transaction between market participants at the measurement date.

Valuation techniques used to measure fair value must maximize the use of observable inputs and minimize the use of unobservable inputs.

The accounting standard establishes a fair value hierarchy that prioritizes observable and unobservable inputs used to measure fair value into three broad levels, which are described below:

Level 1: Quoted prices (unadjusted) in active markets that are accessible at the measurement date for assets or liabilities. The fair value hierarchy gives the highest priority to Level 1 inputs.

Level 2: Observable inputs that are based on inputs not quoted on active markets but corroborated by market data.

Level 3: Unobservable inputs are used when little or no market data are available.

Restricted bank deposits, trade receivables, trade payables are stated at their carrying value, which approximates fair value due to the short time to the expected receipt or payment date.

Research and Development

Research and development costs are expensed as incurred. Research and development costs include payroll and personnel expenses, consulting costs, external contract research and development expenses, raw materials, drug product manufacturing costs, and allocated overhead including depreciation, rent, and utilities. Research and development costs that are paid in advance of performance are classified as a prepaid expense and amortized over the service period as the services are provided.

Acquired In-Process Research and Development

In an asset acquisition, the initial costs of rights to in-process research and development projects acquired are expensed as R&D in the consolidated statements of operations unless the in-process research and development has an alternative future use. In a business combination, the fair value of in-process research and development is capitalized as an indefinite-lived intangible asset, regardless of whether the in-process research and development asset has an alternative future use.

Clinical Trial Costs

Clinical trial costs are a component of research and development expenses. The Company bases its expenses related to Clinical Research Organization (“CRO”) on the services received, and efforts expanded pursuant to agreements with them. The financial terms of these agreements are subject to negotiation, vary from contract to contract and may result in uneven payment flows. In instances where payments made to CROs exceed the level of services provided and result in a prepayment of the research and development expenses. For reoccurring services fees, the Company calculates the time period over which services will be performed and the level of effort to be expanded in each period. If the actual timing of the performance of services varies from the calculation, the Company adjusts the accrual or amount of prepaid expenses accordingly. Non-refundable advance payments for goods and services that will be used in future research and development activities are expensed when the activity has been performed or when the goods have been received rather than when the payment is made.

Patent Costs

Legal and related patent costs are expensed as incurred as their realization is uncertain. Costs related to patent registration are classified as general and administrative expenses, and costs related to acquired patents are classified as research and development expenses in the accompanying consolidated statements of operations.

Contingent Liabilities

The Company accounts for its contingent liabilities in accordance with ASC No. 450, “Contingencies”. A provision is recorded when it is both probable that a liability has been incurred and the amount of the loss can be reasonably estimated. With respect to legal matters, provisions are reviewed and adjusted to reflect the impact of negotiations, estimated settlements, legal rulings, advice of legal counsel and other information and events pertaining to a particular matter. As of December 31, 2021, and 2020, the Company is not a party to any litigation that could have a material adverse effect on the Company’s business, financial position, results of operations or cash flows.

Income Taxes

The Company accounts for income taxes in accordance with ASC 740, “Income Taxes”. This standard prescribes the use of the liability method whereby deferred tax asset and liability account balances are determined based on differences between financial reporting and tax bases of assets and liabilities and are measured using the enacted tax rates and laws that will be in effect when the differences are expected to reverse. The Company provides a valuation allowance, if necessary, to reduce deferred tax assets to their estimated realizable value, if it is more likely than not that some portion of the entire deferred tax asset will not be realized.

The Company accounts for uncertain tax positions in accordance with the provisions of ASC 740-10, “Income Taxes”. Accounting guidance addresses the determination of whether tax benefits claimed or expected to be claimed on a tax return should be recorded in the consolidated financial statements, under which a Company may recognize the tax benefit from an uncertain tax position only if it is more likely than not that the tax position will be sustained on examination by the taxing authorities, based on the technical merits of the position.

The tax benefits recognized in the consolidated financial statements from such a position should be measured based on the largest benefit that has a greater than fifty percent likelihood of being realized upon ultimate settlement.

Concentrations of Credit Risk

Financial instruments that potentially subject the Company to a concentration of credit risk consist primarily of cash and cash equivalents. Bank deposits are held by accredited financial institutions and these deposits may at times be in excess of insured limits. Money Market funds are of Prime A and only invested in government issued securities. The Company limits its credit risk associated with cash and cash equivalents by placing them with financial institutions that it believes are of high-quality credit rating. The Company has not experienced any losses on its deposits of cash or cash equivalents.

Company's trade receivables are from one customer as of December 31, 2021, and December 31, 2020. In addition, the potential risk of loss with any one counterparty resulting from this type of credit risk is monitored on an ongoing basis. The Company grants credit of 45 days to this one customer.

Stock-Based Compensation

The Company measures its stock-based payment awards made to employees, directors, and non-employee service providers based on estimated fair values. The fair value of each option award is estimated on the grant date using the Black-Scholes option pricing model. The Company recognizes compensation expenses based on the accelerated method over the requisite service period. The Company recognizes forfeitures of awards as they occur.

The Black-Scholes option pricing model requires a number of assumptions, of which the most significant are share price, expected volatility, expected option term (the time from the grant date until the options are exercised or expire), risk-free rate, and expected divided rate. Share price is estimated based on third party valuation (see also Note 9). After the IPO, the fair value of each ordinary share was based on the closing price of the Company's publicly traded ordinary shares as reported on the date of the grant.

Expected volatility

As the Company has a short trading history for its ordinary shares, the expected volatility is derived from the average historical share volatilities of several unrelated public companies within the Company's industry that the Company considers to be comparable to its own business over a period equivalent to the option's expected term.

Expected Dividend Yield

The Company has historically not paid dividends and has no foreseeable plans to pay dividends, therefore the Company uses an expected dividend yield of 0%.

Risk-Free Interest Rate

The risk-free interest rate is based on the yield from U.S. Treasury zero-coupon bonds with an equivalent expected term.

Expected Term The expected option term is calculated for options granted to employees and directors using the "simplified" method. Under this approach, the expected term is presumed to be the midpoint between the weighted average vesting term and the contractual term of the option. The simplified method makes the assumption that the employee will exercise share options evenly over the period when the share options are vested and ending on the date when the share options expire. The expected option term for options granted to non-employees is based on the contractual term. Changes in the determination of each of the inputs can affect the fair value of the share options granted and the results of operations of the Company.

Restricted shares are value as fair value of shares on date of grant.

Basic and Diluted Net Loss per Share

Basic loss per share is computed by dividing the net loss by the weighted average number of shares of Common Stock outstanding during the period. Diluted loss per share is computed by dividing the net loss by the weighted average number of shares of Common Stock outstanding together with the number of additional shares of Common Stock that would have been outstanding if all potentially dilutive shares of Common Stock had been issued. Diluted net loss per share is the same as basic net loss per share in periods when the effects of potentially dilutive shares of Common Stock are anti-dilutive.

Segment Information

Financial information is available for evaluation by the chief operating decision maker, the Company's Chief Executive Officer, in making decisions regarding resource allocation and assessing performance. The Company views its operations and manages its business in one operating segment. Operating segments are defined as components of an enterprise in which separate financial information is evaluated regularly by the chief operating decision maker in deciding how to allocate resources and assessing performance.

Revenue Recognition

The Company recognizes revenue in accordance with ASC Topic 606, Revenue from Contracts with Customers, which applies to all contracts with customers. Under Topic 606, an entity recognizes revenue when its customer obtains control of promised goods or services, in an amount that reflects the consideration that the entity expects to receive in exchange for those goods or services. To determine revenue recognition for arrangements that an entity determines are within the scope of Topic 606, the entity performs the following five steps:

(i) identify the contract(s) with a customer;

(ii) identify the performance obligations in the contract;

(iii) determine the transaction price;

(iv) allocate the transaction price to the performance obligations in the contract; and

(v) recognize revenue when (or as) the entity satisfies a performance obligation.

At contract inception, once the contract is determined to be within the scope of Topic 606, the Company assesses the goods or services promised within the contract and determines those that are performance obligations and assesses whether each promised good or service is distinct.

Customer option to acquire additional goods or services gives rise to a performance obligation in the contract only if the option provides a material right to the customer that it would not receive without entering into that contract.

In a contract with multiple performance obligations, the Company must develop estimates and assumptions that require judgment to determine the underlying stand-alone selling price for each performance obligation, which determines how the transaction price is allocated among the performance obligations.

The Company evaluates each performance obligation to determine if it can be satisfied at a point in time or over time.

Revenue is recognized when control of the promised goods or services is transferred to the customers, in an amount that reflects the consideration the Company expect to be entitled to receive in exchange for those goods or services.

In December 2018, the Company entered into an Evaluation Option to acquire License Agreement (the "Novartis Agreement") with Novartis International Pharmaceutical Limited ("Novartis") for which the company is paid for its research and development costs. For additional details regarding the Novartis Agreement, refer to Note 5.

The Company concluded that there is one distinct performance obligation under the Novartis Agreement: Research and development services, obligation which is satisfied over time.

Revenue associated with the research and development services in the amount of $3.5 million and $3.7 million was recognized in 2021 and 2020 respectively.

The Company concluded that progress towards completion of the research and development performance obligation related to the Novartis Agreement is best measured in an amount proportional to the expenses incurred from the total estimated expenses. The Company periodically reviews and updates its estimates, when appropriate, which may adjust revenue recognized for the period. The transaction price to be recognized as revenue under the Novartis Agreement consists of the reimbursable research and development costs.

Recently Issued Accounting Pronouncements Not Yet Adopted

As an "emerging growth company," the Jumpstart Our Business Startups Act ("JOBS Act") allows the Company to delay adoption of new or revised accounting pronouncements applicable to public companies until such pronouncements are made applicable to private companies. The Company has elected to use this extended transition period under the JOBS Act. The adoption dates discussed below reflects this election.

In February 2016, the FASB issued ASU 2016-02—Leases, requiring the recognition of lease assets and liabilities on the balance sheet. The standard: (a) clarifies the definition of a lease; (b) requires a dual approach to lease classification similar to current lease classifications; and (c) causes lessees to recognize leases on the balance sheet as a lease liability with a corresponding right-of-use asset for leases with a lease-term of more than 12 months. The standard will be effective for the Company for fiscal years beginning after December 15, 2021. The Company is currently evaluating the impact of adopting this new guidance on its financial statements.

In June 2016, the FASB issued ASU No. 2016-13 (Topic 326), Financial Instruments—Credit Losses: Measurement of Credit Losses on Financial Instruments, which replaces the existing incurred loss impairment model with an expected credit loss model and requires a financial asset measured at amortized cost to be presented at the net amount expected to be collected. The guidance will be effective for the Company for fiscal years beginning after December 15, 2022. Early adoption is permitted. The Company is currently evaluating the effect that ASU 2016-13 will have on its consolidated financial statements and related disclosures.

In August 2020, the FASB issued ASU 2020-06, Debt - Debt with Conversion and Other Options (Subtopic 470-20) and Derivatives and Hedging - Contracts in Entity's Own Equity (Subtopic 815-40): Accounting for Convertible Instruments and Contracts in an Entity's Own Equity ("ASU 2020-06"). The final guidance issued by the FASB for convertible instruments eliminates two of the three models in ASC 470-20 that require separate accounting for embedded conversion features. Separate accounting is still required in certain cases. Additionally, among other changes, the guidance eliminates some of the conditions for equity classification in ASC 815-40-25 for contracts in an entity's own equity. The guidance also requires entities to use the if-converted method for all convertible instruments in the diluted earnings per share calculation and include the effect of share settlement for instruments that may be settled in cash or shares, except for certain liability-classified share-based payment awards. ASU 2020-06 is effective for fiscal years beginning after December 15, 2023, and interim periods within those fiscal years. The Company is currently evaluating the potential impact of this guidance on its consolidated financial statements.

3. Property and Equipment, net

Property and Equipment, net consists of the following:

	December 31, 2021	December 31, 2020
	(in thousands)	
Cost:		
Computers and Software	$ 73	$ 73
Lab Equipment	294	293
Office Furniture and Equipment	146	142
Leasehold Improvements	1,105	1,105
	1,618	**1,613**
Less: Accumulated Depreciation	498	330
Property and Equipment, Net	**$ 1,120**	**$ 1,283**

Depreciation expenses for the years ended December 31, 2021, and 2020 was approximately $168 and $182, respectively.

4. Other account payables

Other account payables consist of the following:

	December 31, 2021	December 31, 2020
	(in thousands)	
Accrued Professional Fees	$ 291	$ 657
Accrued Research and Development Expenses	56	101
Tax Provision	1,150	780
Accrued Payroll and Employee Benefits	1,761	1,613
Total Accrued Expenses	$ 3,258	$ 3,151

5. Commitments and Contingent Liabilities

Lease

The Subsidiary rents its facilities under an operating lease agreement, which expired in November 2019.

In January 2019, the Company signed a new lease agreement. The term of the lease is for 63 months and includes an option to extend the lease for an additional 60 months. As part of the agreement, the lessor also provided the Company with finance in in the amount of approximately $0.5 million paid in arrears for of leasehold improvements. The financing was recorded as a Long-Term Rent Liability. The minimum rental payments under operating leases as of December 31, 2021, are as follows (in thousands):

Year ended December 31,	(in thousands)
2022	360
2023	360
2024	120
	$ 840

The Subsidiary obtained a bank guarantee in the amount of approximately $0.2 million for its new office lease agreement.

The subsidiary leasing expense for the years ended December 2021 and 2020 was $0.3 million and $0.3 million, respectively.

Asset Transfer and License Agreement with Bristol-Myers Squibb Company.

In November 2017, the Company entered into a license agreement, or the BMS License Agreement, with Bristol-Myers Squibb Company, or BMS, under which BMS granted the Company a worldwide, non-transferable, exclusive, sublicensable license under certain patent rights and know-how controlled by BMS to research, discover, develop, make, have made, use, sell, offer to sell, export, import and commercialize AL101 and AL102, or the BMS Licensed Compounds, and products containing AL101 or AL102, or the BMS Licensed Products, for all uses including the prevention, treatment or control of any human or animal disease, disorder or condition.

Under the BMS License Agreement, the Company is obligated to use commercially reasonable efforts to develop at least one BMS Licensed Product. The Company has sole responsibility for, and bear the cost of, conducting research and development and preparing all regulatory filings and related submissions with respect to the BMS Licensed Compounds and/or BMS Licensed Products. BMS has assigned and transferred all INDs for the BMS Licensed Compounds to the Company. The Company is also required to use commercially reasonable efforts to obtain regulatory approvals in certain major market countries for at least one BMS Licensed Product, as well as to effect the first commercial sale of and commercialize each BMS Licensed Product after obtaining such regulatory approval. The Company has sole responsibility for, and bear the cost of, commercializing BMS Licensed Products. For a limited period of time, the Company may not, engage directly or indirectly in the clinical development or commercialization of a Notch inhibitor molecule that is not a BMS Licensed Compound.

As consideration of the rights granted by BMS to the Company under the BMS License Agreement, the Company paid BMS a payment of $6 million and issued to BMS 1,125,929 shares of Series A Preferred Stock valued at approximately $7.3 million. The payment and transfer of intellectual property occurred in November 2017 at the time the BMS License Agreement was executed (the "Effective Date").

The Company is required to pay BMS payments upon the achievement of certain development or regulatory milestone events of up to $95 million in the aggregate with respect to the first BMS Licensed Compound to achieve each such event and up to $47 million in the aggregate with respect to each additional BMS Licensed Compound to achieve each such event. The Company is also obligated to pay BMS payments of up to $50 million in the aggregate for each BMS Licensed Product that achieves certain sales-based milestone events and tiered royalties on net sales of each BMS Licensed Product by the Company or its affiliates or sublicensees at rates ranging from a high single-digit to low teen percentage, depending on the total annual worldwide net sales of each such Licensed Product. If the Company sublicenses or assigns any rights to the licensed patents, the BMS Licensed Compounds and/or the BMS Licensed Products, the Company is required to share with BMS a portion of all consideration received from such sublicense or assignment, ranging from a mid-teen to mid-double-digit percentage, depending on the development stage of the most advanced BMS Licensed Compound or BMS Licensed Product that is subject to the applicable sublicense or assignment, but such portion may be reduced based on the milestone or royalty payments that are payable by the Company to BMS under the BMS License Agreement.

Under the terms of the BMS Agreement, the Company was obligated to issue to BMS additional shares of preferred stock as would be required for BMS to maintain its 8% equity ownership in Company, subject to certain exceptions. This right terminated upon the closing of the sale of the Company's Series B Preferred Stock. The Company estimates the fair value of this anti-dilution commitment using the probability weighted expected return method ("PWERM"). At the date of BMS Agreement, the Company recorded liability associated with the anti-dilution right in the amount of approximately $0.5 million, according to its fair value. For the year ended December 31, 2018, the Company recorded an income of approximately $0.5 million for the reassessment of the liability, within financial income, net, in the consolidated statement of operations.

The Company accounted for the acquisition of the rights granted by BMS as an asset acquisition because it did not meet the definition of a business. The Company recorded the total consideration transferred and value of shares issued to BMS as research and development expense in the consolidated statement of operations as incurred since the acquired the rights granted by BMS represented in-process research and development and had no alternative future use.

The Company accounts for contingent consideration payable upon achievement of sales milestones in such asset acquisitions when the underlying contingency is resolved.

The BMS License Agreement remains in effect, on a country-by-country and BMS Licensed Product-by-BMS Licensed Product basis, until the expiration of royalty obligations with respect to a given BMS Licensed Product in the applicable country. Royalties are paid on a country-by-country and BMS Licensed Product-by-BMS Licensed Product basis from the first commercial sale of a particular BMS Licensed Product in a country until the latest of

10 years after the first commercial sale of such BMS Licensed Product in such country, (b) when such BMS Licensed Product is no longer covered by a valid claim in the licensed patent rights in such country, or (c) the expiration of any regulatory or marketing exclusivity for such BMS Licensed Product in such country. Any inventions, and related patent rights, invented solely by either party pursuant to activities conducted under the BMS License Agreement shall be solely owned by such party, and any inventions, and related patent rights, conceived of jointly by the Company and BMS pursuant to activities conducted under the BMS License Agreement shall be jointly owned by the Company and BMS, with BMS's rights thereto included in the Company's exclusive license. The Company has the first right—with reasonable consultation with, or participation by, BMS—to prepare, prosecute, maintain and enforce the licensed patents, at the Company's expense.

BMS has the right to terminate the BMS License Agreement in its entirety upon written notice to the Company (a) for insolvency-related events involving the Company, (b) for the Company's material breach of the BMS License Agreement if such breach remains uncured for a defined period of time, for the Company's failure to fulfill its obligations to develop or commercialize the BMS Licensed Compounds and/or BMS Licensed Products not remedied within a defined period of time following written notice by BMS, or (d) if the Company or its affiliates commence any action challenging the validity, scope, enforceability or patentability of any of the licensed patent rights. The Company has the right to terminate the BMS License Agreement for convenience upon prior written notice to BMS, the length of notice dependent on whether a BMS Licensed Project has received regulatory approval, (b) upon immediate written notice to BMS for insolvency-related events involving BMS, (c) for BMS's material breach of the BMS License Agreement if such breach remains uncured for a defined period of time, or (d) on a BMS Licensed Compound-by-BMS Licensed Compound and/or BMS Licensed Product-by-BMS Licensed Product basis upon immediate written notice to BMS if the Company reasonably determine that there are unexpected safety and public health issues relating to the applicable BMS Licensed Compounds and/or BMS Licensed Products.

Upon termination of the BMS License Agreement in its entirety by the Company for convenience or by BMS, the Company grants an exclusive, non-transferable, sublicensable, worldwide license to BMS under certain of its patent rights that are necessary to develop, manufacture or commercialize BMS Licensed Compounds or BMS Licensed Products. In exchange for such license, BMS must pay the Company a low single-digit percentage royalty on net sales of the BMS Licensed Compounds and/or BMS Licensed Products by it or its affiliates, licensees or sublicensees, provided that the termination occurred after a specified developmental milestone for such BMS Licensed Compounds and/ or BMS Licensed Products.

Option and License Agreement with Novartis International Pharmaceutical Ltd.

In December 2018, the Company entered into an evaluation, option and license agreement, or the Novartis Option Agreement, with Novartis International Pharmaceutical Limited, or Novartis, pursuant to which Novartis agreed to conduct certain studies to evaluate AL102 in combination with its B-cell maturation antigen, or BCMA, therapies in multiple myeloma, and the Company agreed to supply AL102 for such studies. All supply and development costs associated with such evaluation studies are fully borne by Novartis.

Under the Novartis Option Agreement, the Company granted Novartis an exclusive option to obtain an exclusive (including as to the Company and its affiliates), sublicensable (subject to certain terms and conditions), worldwide license and sublicense (as applicable) under certain patent rights and know-how controlled by the Company (including applicable patent rights and know-how that are licensed from BMS pursuant to the BMS License Agreement) to research, develop, manufacture (subject to the Company's non-exclusive right to manufacture and supply AL102 or the Novartis Licensed Product for Novartis) and commercialize AL102 or any pharmaceutical product containing AL102 as the sole active ingredient, or the Novartis Licensed Product, for the diagnosis, prophylaxis, treatment, or prevention of multiple myeloma in humans. The Company also granted Novartis the right of first negotiation for the license rights to conduct development or commercialization activities with respect to the use of AL102 for indications other than multiple myeloma. Additionally, from the exercise by Novartis of its option until the termination of the Novartis Option Agreement, the Company may not, either itself or through its affiliates or any other third parties, directly or indirectly research, develop or commercialize certain BCMA-related compounds for the treatment of multiple myeloma.

According to the agreement, Novartis shall pay the Company a low eight figure option exercise fee in order to exercise its option and activate its license, upon which the Company will be eligible to receive development, regulatory and commercial milestone payments of up to $245 million in the aggregate and tiered royalties on net sales of Novartis Licensed Products by Novartis or its affiliates or sublicensees at rates ranging from a mid-single-digit to low double-digit percentage, depending on the total annual worldwide net sales of Novartis Licensed Products. Royalties will be paid on a country-by-country and Novartis Licensed Product-by-Novartis

Licensed Product basis from the first commercial sale of a particular Novartis Licensed Product in a country until the latest of (a) 10 years after the first commercial sale of such Novartis Licensed Product in such country, (b) when such Novartis Licensed Product is no longer covered by a valid claim in the licensed patent rights in such country, or (c) the expiration of any regulatory or marketing exclusivity for such Novartis Licensed Product in such country. Contemporaneously with the Novartis Option Agreement, the Company entered into a stock purchase agreement and associated investment agreements, or the SPA, with Novartis' affiliate, Novartis Institutes for BioMedical Research, Inc., or NIBRI, pursuant to which NIBRI acquired a $10 million equity stake in the Company.

Novartis shall own any inventions, and related patent rights, invented solely by it or jointly with the Company in connection with activities conducted pursuant to the Novartis Option Agreement. The Company will maintain first right to prosecute and maintain any patents licensed to Novartis, both before and after its exercise of its option. The Company maintain the first right to defend and enforce its patents prior to Novartis's exercise of its option, upon which Novartis gains such right with respect to patents included in the license.

The option granted to Novartis will remain in effect until the earlier of (a) 60 days following the last visit of the last subject in the evaluation studies, the termination of the Novartis Option Agreement, or (c) 36 months following the delivery by the Company to Novartis of sufficient amounts of clinical evaluation materials to conduct the anticipated clinical studies. The Novartis Option Agreement remains in effect until such time as no Novartis Licensed Product is being developed or commercialized by Novartis, its affiliates, or sublicensees (including distributors or commercial partners), unless terminated earlier. The Company has the right to terminate the Novartis Option Agreement (a) for Novartis's material breach if such breach remains uncured for 60 days (such cure period shall be extended for an additional period during which Novartis is making good faith efforts to cure such breach) or (b) for Novartis's failure to use commercially reasonable efforts to develop or commercialize AL102 and/or the Novartis Licensed Product not remedied within four months following written notice to Novartis. Novartis has the right to terminate the Novartis Option Agreement (a) in its entirety or on a country-by-country basis for convenience, upon 60 days written notice to us, (b) for Company's material breach if such breach remains uncured for 60 days (such cure period shall be extended for an additional period during which Novartis is making good faith efforts to cure such breach) or (c) upon immediate written notice to the Company for insolvency-related events involving the Company.

6. Fair Value Measurements

As of December 31, 2021, the Company had no financial liabilities measured at fair value.

The following tables summarize the fair value measurements of our financial instruments as of December 31, 2021:

	Fair Value Measurements at December 31, 2021			
	Quoted Prices in Active Markets for Identical Assets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)	Total
		($in thousands)		
Cash equivalents:				
Money market funds	$ 32,900	$ —	$ —	$ 32,900
Total cash equivalents	$ 32,900	$ —	$ —	$ 32,900

The following tables summarize the fair value measurements of our financial instruments as of December 31, 2020:

	Fair Value Measurements at December 31, 2020			
	Quoted Prices in Active Markets for Identical Assets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)	Total
		($in thousands)		
Cash equivalents:				
Money market funds	$ 35,900	$ —	$ —	$ 35,900
Total cash equivalents	$ 35,900	$ —	$ —	$ 35,900

7. Common Stock

The Common Stock confer upon the holders the right vote in annual and special meetings of the Company, and to participate in the distribution of the surplus assets of the Company upon liquidation of the Company, after the distribution of the preferred stock liquidation preference. No dividends have been declared as of December 31, 2021 and 2020.

On May 12, 2020, the Company completed the sale of shares of its Common Stock in its IPO. In connection with the IPO, the Company issued and sold 3,940,689 shares of Common Stock, including 274,022 shares associated with the partial exercise on June 4, 2020 of the underwriters' option to purchase additional shares, at a price to the public of $15.00 per share, resulting in net proceeds to the Company of approximately $52.8 million after deducting underwriting discounts and commissions and estimated offering expenses payable by the Company. All shares issued and sold were registered pursuant to a registration statement on Form S-1 (File No. 333-236942), as amended, declared effective by the U.S. Securities and Exchange Commission (the "Commission") on May 7, 2020.

In connection with the IPO, the Company effected a one-for-two reverse stock split of its Common Stock which became effective on May 4, 2020. Upon the closing of the IPO, all of the outstanding shares of Series A preferred stock and Series B preferred stock automatically converted into an aggregate of 3,715,222 shares of Common Stock . Subsequent to the closing of the IPO, there were no shares of preferred stock outstanding, and amended the authorized capital stock of the company to (i) 200,000,000 shares of Common Stock (ii) 10,000,000 shares of Preferred Stock.

On February 19, 2021, we entered into a Securities Purchase Agreement (the "2021 Purchase Agreement") with the purchasers named therein (the "Investors"). Pursuant to the 2021 Purchase Agreement, we agreed to issue (i) an aggregate of 333,333 shares of our common stock (the "Private Placement Shares"), par value $0.01 per share, together with warrants to purchase an aggregate of 116,666 shares of our common stock with an exercise price of $18.10 per share (the "Common Warrants"), for an aggregate purchase price of $4,999,995.00 and (ii) pre-funded warrants to purchase an aggregate of 1,333,333 shares of our common stock with an exercise price of $0.01 per share (the "Pre-Funded Warrants" and collectively with the Common Warrants, the "Private Placement Warrants"), together with an aggregate of 466,666 Common Warrants, for an aggregate purchase price of $19,986,661.67 (collectively, the "Private Placement"). The Private Placement closed on February 23, 2021. The Company had issuance costs of approximately $1.715 million. The Private Placement closed on February 23, 2021. The warrants were classified as a component of permanent equity pursuant to ASC 480 "Distinguishing Liabilities from Equity" and ASC 815 "Derivatives and Hedging." As of December 31, 2021, the 1,799,999 warrants are all outstanding.

In June 2021, we entered into an Open Market Sales Agreement, or the Sales Agreement, with Jefferies LLC, or Jefferies, as sales agent, pursuant to which we may, from time to time, issue and sell common stock with an aggregate value of up to $200.0 million in "at-the-market" offerings, under our Registration Statement on Form S-3 (File No. 333-256792) filed with the SEC on June 4, 2021 (the "ATM"). Sales of common stock, if any, pursuant to the Sales Agreement, may be made in sales deemed to be an "at the market offering" as defined in Rule 415(a) of the Securities Act, including sales made directly through The Nasdaq Global Market or on any other existing trading market for our common stock. Pursuant to the Sales Agreement, during the twelve months ended December 31, 2021, the Company issued a total of 827,094 shares of common stock for total gross proceeds of approximately $10.4 million.

Total shares of Common Stock reserved for issuance are summarized as follows:

	December 31, 2021	December 31, 2020
Options Outstanding	900,789	695,674
Warrants for common shares of the company.	1,799,999	
Shares available for future option grants	593,040	387,736
Total shares of Common Stock reserved for Issuance	3,293,828	1,083,410

Composition of Capital Stock:

	December 31, 2021		December 31, 2020	
	Authorized	Issued and outstanding	Authorized	Issued and outstanding
Shares of USD 0.01 par value:				
Common Stock	200,000,000	13,956,035*	200,000,000	12,728,446*

* Does not include 124,348 and 96,017 shares of restricted Common Stock issued but not outstanding in 2021 and 2020, respectively.

8. Stock-Based Plans

In 2017, the Company's board of directors adopted the 2017 Stock Incentive Plan (the "Plan"). According to the Plan, share awards, including restricted stock, restricted stock units or other stock-based awards, or options to purchase shares may be granted to employees, directors, consultants and other service providers of the Company or any affiliate of the Company.

As of December 31, 2021, a total of 1,841,040 shares of Common Stock were authorized for issuance in accordance with the provisions of the 2017 Plan, of which 593,040 shares were then available for future awards (whether as share awards or as options to purchase shares of common stock of the Company). Each option granted under the Plan expires no later than 10 years from the date of grant. The options vest primarily over four to five years of employment.

The following table set forth the parameters used in the computation of the fair value of options granted to employees:

	Year ended December 31,	
	2021	2020
Expected volatility	80%	80%
Expected dividends	0%	0%
Expected term (in years)	6.34	6.34
Risk free rate	0.50%-1.08%	0.47%-2.03%

Expected Volatility:

As the Company was privately owned in part of 2020, there was not sufficient historical volatility for the expected term of the stock options. Therefore, the Company used an average historical share price volatility based on an analysis of reported data for a peer group of comparable publicly traded companies which were selected based upon industry similarities.

Expected term (years):

Expected term represents the period that the Company's option grants are expected to be outstanding. There is not sufficient historical share exercise data to calculate the expected term of the stock options. Therefore, the Company elected to utilize the simplified method to value option grants. Under this approach, the weighted-average expected life is presumed to be the average of the shortest vesting term and the contractual term of the option.

Risk-free interest rate:

The Company determined the risk-free interest rate by using a weighted-average equivalent to the expected term based on the U.S. Treasury yield curve in effect as of the date of grant.

Expected dividend yield:

The Company does not anticipate paying any dividends in the foreseeable future.

The Company recorded stock-based compensation for the period indicated as follows (in thousands):

	Year ended December 31, 2021	Year ended December 31, 2020
Research and Development	$ 1,097	$ 509
General and Administrative	1,587	1,060
Total Stock-Based Compensation	$ 2,684	$ 1,569

The Company recognizes compensation expenses for the value of its awards granted based on the accelerated method over the requisite service period of each of the awards.

A summary of the Company's stock option activity granted to employees under the Plan is as follows:

	Year ended December 31, 2021			
	Number of options	Weighted average exercise price	Weighted average remaining contractual term (in years)	Aggregate intrinsic value
Outstanding at Beginning of Year	695,674	$ 6.07	7.25	$ 1,695,276
Granted	295,470	10.99		
Exercised	(18,328)	5.50		$ 55,133
Forfeited	(70,527)	9.78		
Expired	(1,500)	5.10		
Outstanding, December 31, 2021	900,789	$ 7.41	7.78	$ 991,878
Exercisable Options, December 31, 2021	476,303	$ 5.93	7.12	$ 1,230,643

The weighted-average grant date per-share fair value of stock options granted during 2021 and 2020 was $7.98 and $6.07, respectively. The aggregate intrinsic value of stock options exercised during the year ended December 31, 2021 and 2020 was $55 and $280, respectively. As of December 31, 2021, there was approximately $ 1.1 million of total unrecognized compensation cost related to non-vested stock-based compensation arrangements granted under the Plan. That cost is expected to be recognized over a weighted-average period of 0.93 years.

Company's restricted shares:

In February 2018, the Company granted 83,165 restricted shares to an employee and an officer of the Company. In the case of the officer, the restricted shares vest over two years starting November 15, 2017, and in the case of the other employee, the restricted shares vest over four years starting November 15, 2017.

In December 2019, the Company granted 59,597 restricted shares to two officers of the Company. The restricted shares vest over four years starting December 24, 2019.

In May 2020, the Company granted 58,651 restricted shares to two officers of the Company. The restricted shares vest over four years starting May 7, 2020.

The following table summarizes information relating to restricted shares, as well as changes to such awards during the fiscal years ended December 31, 2021 and 2020:

	Year ended December 31, 2021	Year ended December 31, 2020
Outstanding at beginning of Year	101,929	65,847
Granted	71,253	58,651
Forfeited	—	(3,907)
Vested	(48,834)	(18,662)
Outstanding at end of Year	124,348	101,929

The weighted average fair values at grant date of restricted shares granted for the years ended December 31, 2021 and 2020 was $11.26 and $15.00, per share respectively.

The total fair value of shares vested during each of 2021 and 2020 was approximately $0.2 million. As of December 31, 2021, the Company had approximately $1.8 million of unrecognized compensation expense related to non-vested restricted shares, expected to be recognized over a weighted average period of 1.73 years.

Restricted shares are subject to a repurchase right by the Company on certain occasions. Under the repurchase right, the Company may reacquire restricted shares, for no consideration, if certain conditions occur including the employees' end of service with the Company.

9. Taxes on Income

The Company records income tax expense related to profits realized in the United States and realized by its subsidiary in Israel.

United States:

On December 22, 2017, the United States enacted the Tax Cuts and Jobs Act (the "U.S. Tax Reform"); a comprehensive tax legislation that includes significant changes to the taxation of business entities. These changes, most of which are effective for tax years beginning after December 31, 2017, include several key tax provisions that might impact the Company, among others: (i) a permanent reduction to the statutory federal corporate income tax rate from 35% (top rate) to 21% (flat rate) effective for tax years beginning after December 31, 2017 (ii) a new tax deduction in the amount of 37.5% of "foreign derived intangible income" that effectively reduces the federal corporate tax on certain qualified foreign derived sales/licenses/leases and service income in excess of a base amount to 13.125% (as compared to the regular corporate income tax rate of 21%); (iii) stricter limitation on the tax deductibility of business interest expense; (iv) a shift of the U.S. taxation of multinational corporations from a tax on worldwide income to a territorial system (along with certain rules designed to prevent erosion of the U.S. income tax base) (v) a one-time deemed repatriation tax on accumulated offshore earnings held in cash and illiquid assets, with the latter taxed at a lower rate and (vi) an expansion of the U.S. controlled foreign corporation ("CFC") anti deferral starting with the CFC's first tax year beginning in 2018 intended to tax in the U.S. "global intangible low-taxed income" ("GILTI").

The Company recorded loss from continuing operations, before taxes on income for the period indicated as follows (in thousands):

	Year ended December 31, 2021	Year ended December 31, 2020
United States	$ (39,018)	$ (29,698)
Israel	(460)	(23)
Net loss before tax	$ (39,478)	$ (29,721)

Income tax expense is summarized as follows (in thousands):

	Year ended December 31, 2021	Year ended December 31, 2020
Current:		
Federal	$ —	$
State		—
Foreign	776	426
	$ 776	$ 426
Deferred:		
Federal	$ —	$ —
State	—	—
Foreign	—	—
	$ —	$ —
Income tax expense	$ 776	$ 426

The effective income tax rate differed from the amount computed by applying the federal statutory rate to our loss before income taxes as follows:

	Year ended December, 31 2021	Year ended December, 31 2020
U.S. federal tax provision at statutory rate	21.00%	21.00%
State and local tax, net of federal benefit	4.01	4.64
Foreign rate differences	(0.09)	(0.07)
Non-deductible stock compensation	(1.43)	(1.11)
Section 951A GILTI	0.00	(0.85)
Effect of other permanent differences	(0.07)	(0.07)
Uncertain tax positions	(0.66)	(0.52)
Change in valuation allowance	(34.39)	(26.65)
Federal Tax Reform Rate Change	0.00	0.00
Tax Credits	6.01	—
Provision to Return	3.95	—
Other adjustments	(0.30)	2.20
Effective tax rate	(1.97)%	(1.43)%

Deferred Income Taxes

Deferred income taxes reflect the net tax effects of temporary differences between the carrying amounts of assets and liabilities for financial reporting purposes and the amounts used for income tax purposes. Significant components of the Company's deferred tax assets are as follows (in thousands):

	As of December 31, 2021	As of December 31, 2020
Deferred tax assets:		
Federal net operating loss carryforwards	$ 22,614	$ 12,752
Intangible assets	3,402	651
Accrued expenses	3,011	3,022
Other	169	—
Total deferred tax assets	29,196	16,425
Valuation allowance	(29,196)	(16,425)
Net deferred tax assets	$ —	$ —

As of December 31, 2021, the Company has provided a valuation allowance of approximately $29.2 million in respect of the Company's deferred tax assets resulting from tax loss carryforwards and other temporary differences. Realization of deferred tax assets is dependent upon future earnings, if any, the time and amount of which are uncertain. As the Company is still in its development stage and has not yet generated revenues, it is more likely than not that sufficient taxable income will not be available for the tax losses to be utilized in the future. Therefore, a valuation allowance was recorded to reduce the deferred tax assets to their recoverable amounts.

Available Carryforward Tax Losses

As of December 31, 2021, we had net operating loss carryforwards, or NOLs, of $91.6 million for federal income tax purposes and $57.7 million for state income tax purposes, which may be available to offset our future taxable income, if any, and begin to expire in various amounts in 2037 and 2038, respectively, provided that NOLs generated in tax years ending after December 31, 2017 will not be subject to expiration. In general, under Sections 382 and 383 of the U.S. 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 use its pre-change NOLs to offset future taxable income. If the U.S. Internal Revenue Service challenges our determinations with respect to the existence of previous ownership changes or the effects thereof, or if we undergo an ownership change, our ability to use our NOLs could be limited by Section 382 of the Code. Future changes in our stock ownership, some of which are outside of our control, could also result in an ownership change under Sections 382 and 383 of the Code. In addition, for taxable years beginning after December 31, 2020, utilization of federal NOLs generated in tax years beginning after December 31, 2017 are limited to a maximum of 80% of the taxable income for such year, after taking into account utilization of NOLs generated in years beginning before January 1, 2018 and determined without regard to such NOL deduction. Furthermore, our ability to use NOLs of companies that we may acquire in the future may be subject to limitations. For these reasons, we may not be able to use a material portion of the NOLs, even if we attain profitability. The reduction of the corporate tax rate under recently-enacted U.S. tax legislation may cause a reduction in the economic benefit of our NOLs and other deferred tax assets available to us.

In addition, as of December 31, 2021, the Company had federal Orphan Drug research and development credit carryforwards of approximately $618 thousand and $33, respectively. If not utilized, the federal tax carryforwards which expire in 2039.

Uncertain Tax Positions

The Company has reviewed the tax positions taken, or to be taken, in our tax returns for all tax years currently open to examination by a taxing authority. As of December 31, 2021, and 2020, the Company has recorded an uncertain tax position liability exclusive of interest and penalties of approximately $0.9 and $0.6 million, respectively. As of December 31, 2021, the Company has not accrued penalties for uncertain tax positions. A reconciliation of the Company's unrecognized tax benefits is below:

	2021 (in thousands)	2020 (in thousands)
Uncertain tax position at the beginning of year	$ 581	$ 424
Additions for uncertain tax position of prior years (foreign exchange and interest)	17	3
Additions for tax positions of current year	260	153
Uncertain tax position at the end of the year	$ 858	$ 581

The Company remains subject to examination until the statute of limitations expires for each respective tax jurisdiction. The statute of limitations is currently open for 2017, 2018, 2019, 2020 and 2021 for all tax jurisdictions.

Israel:

In December 2016, the Israeli Parliament approved the Economic Efficiency Law (Legislative Amendments for Applying the Economic Policy for the 2017 and 2018 Budget Years) which reduces the corporate income tax rate from 25% to 24% effective from January 1, 2017, and to 23% effective from January 1, 2018.

The Israeli corporate income tax rate was 23% in 2021 and 2020. Income not eligible for Preferred Enterprise benefits is taxed at the regular corporate tax rates as described above.

10. Net Loss Per Share Attributable to Common Stockholders

The following table sets forth the computation of the loss per share for the period presented (in thousands, except for share data):

	Year ended December 31, 2021	Year ended December 31, 2020
Numerator:		
Net loss	$ 40,254	$ 30,146
Denominator:		
Weighted-average number of shares used to compute net loss per share, basic and diluted	14,398,905	9,860,610

The calculation of basic and diluted Loss Per Share includes 1,333,333 and 1,155,555 weighted average warrants with an exercise price of $0.01 for the year ended December 31, 2021, respectively.

The following potentially dilutive common stock equivalents have been excluded from the calculation of diluted net loss per share for the period presented due to their anti-dilutive effect: 466,666 shares of common stock and 900,789 options outstanding to purchase common stock as of December 31, 2021.

The following potentially dilutive common stock equivalents have been excluded from the calculation of diluted net loss per share for the period presented due to their anti-dilutive effect: 3,679,778 shares of Series A Preferred Stock, and 3,750,674 shares of Series B Preferred Stock, that were converted on IPO and 695,674 options outstanding to purchase common stock as of December 31, 2020.

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

None.

Item 9A. Controls and Procedures.

Limitations on Effectiveness of Controls and Procedures

In designing and evaluating our disclosure controls and procedures, management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving the desired control objectives. In addition, the design of disclosure controls and procedures must reflect the fact that there are resource constraints and that management is required to apply judgment in evaluating the benefits of possible controls and procedures relative to their costs.

Evaluation of Disclosure Controls and Procedures

Our management, with the participation of our principal executive officer and principal financial officer, evaluated, as of the end of the period covered by this Annual Report on Form 10-K, the effectiveness of our disclosure controls and procedures (as defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act). Based on that evaluation, our principal executive officer and principal financial officer concluded that, as of December 31, 2021, our disclosure controls and procedures were effective at the reasonable assurance level.

Management's Annual Report on Internal Control over Financial Reporting

Our management is responsible for establishing and maintaining adequate internal control over our financial reporting, as such term is defined in Rule 13a-15(f) under the Exchange Act. Our management conducted an assessment of the effectiveness of our internal control over financial reporting based on the criteria set forth in "Internal Control - Integrated Framework (2013)" issued by the Committee of Sponsoring Organizations of the Treadway Commission. Based on this assessment, our management concluded that, as of December 31, 2021, our internal control over financial reporting was effective.

Attestation Report of the Independent Registered Public Accounting Firm

This Annual Report on Form 10-K does not include an attestation report of our independent registered public accounting firm due to an exemption established by the JOBS Act for "emerging growth companies."

Changes in Internal control over Financial Reporting

There were no changes in our internal control over financial reporting (as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act) during the quarter ended December 31, 2021 that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

Item 9B. Other Information.

On November 30, 2021, the board of directors of Ayala Pharmaceuticals, Inc. (the "Company") adopted resolutions (the "Resolutions") approving the ratification of the issuance of certain shares of the Company's common stock, par value $0.01 per share, pursuant to Section 204 of the Delaware General Corporation Law (the "Ratification"). A copy of the Resolutions adopted by the board of directors setting forth the information with respect to the Ratification required under Section 204 of the Delaware General Corporation Law is set forth in Exhibit 99.1 to this Annual Report on Form 10-K. Any claim that any defective corporate act or putative stock ratified pursuant to the Ratification is void or voidable due to the failure of authorization specified in the Resolutions or that the Delaware Court of Chancery should declare in its discretion that the Ratification in accordance with Section 204 of the Delaware General Corporation Law not be effective or be effective only on certain conditions must be brought within 120 days from the giving of this notice (which is deemed to be given on the date that this Annual Report on Form 10-K is filed with the Securities and Exchange Commission).

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

Not applicable.

PART III

Item 10. Directors, Executive Officers and Corporate Governance.

Code of Ethics

Our board of directors has adopted a written Code of Business Conduct and Ethics applicable to all officers, directors and employees, including our principal executive officer, principal financial officer, principal accounting officer or controller, or persons performing similar functions. We have posted a current copy of our Code of Business Conduct and Ethics on our website at www.ayalapharma.com in the "Investors & Media" section under "Corporate Governance." We intend to satisfy the disclosure requirement under Item 5.05 of Form 8-K regarding amendment to, or waiver from, a provision of our Code of Business Conduct and Ethics, as well as The Nasdaq Global Market's requirement to disclose waivers with respect to directors and executive officers, by posting such information on our website at the address and location specified above. The information contained on our website is not incorporated by reference into this Annual Report on Form 10-K.

Executive Officers and Directors

The information concerning our executive offers and directors required by this Item 10 is contained under the caption "Information about our Executive Officers and Directors" at the end of Part I of this Annual Report on Form 10-K. The remainder of the response to this Item 10 will be included in our definitive Proxy Statement for the 2022 Annual Meeting of Stockholders under the headings "Delinquent Section 16(a) Reports" (if applicable) and "Committees of the Board" and is incorporated herein by reference.

Item 11. Executive Compensation.

The information required by this Item 11 will be included in our definitive Proxy Statement for the 2022 Annual Meeting of Stockholders under the headings "Executive and Director Compensation" and "Compensation Committee Interlocks and Insider Participation" (if applicable) and is incorporated herein by reference.

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

The information required by this Item 12 will be included in our definitive Proxy Statement for the 2022 Annual Meeting of Stockholders under the headings "Security Ownership of Certain Beneficial Owners and Management" and "Securities Authorized For Issuance under Equity Compensation Plans" and is incorporated herein by reference.

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

The information required by this Item 13 will be included in our definitive Proxy Statement for the 2022 Annual Meeting of Stockholders under the headings "Corporate Governance" and "Certain Relationships" and is incorporated herein by reference.

Item 14. Principal Accounting Fees and Services.

The information required by this Item 14 will be included in our definitive Proxy Statement for the 2022 Annual Meeting of Stockholders under the heading "Independent Registered Public Accounting Firm Fees and Other Matters" and is incorporated herein by reference.

PART IV

Item 15. Exhibits and Financial Statement Schedules.

(a)(1) Financial Statements.

The financial statements required by this item are listed in Item 8, “Financial Statements and Supplementary Data” herein.

(a)(2) Financial Statement Schedules.

All financial statement schedules have been omitted because they are not applicable, not required or the information required is shown in the financial statements or the notes thereto.

(a)(3) Exhibits.

The following is a list of exhibits filed as part of this Annual Report on Form 10-K.

Exhibit Index

Exhibit Number	Description	Form	File No.	Exhibit	Filing Date	Filed/Furnished Herewith
3.1	Restated Certificate of Incorporation of Ayala Pharmaceuticals, Inc.	8-K	001-39279	3.1	5/12/2020	
3.2	Amended and Restated Bylaws of Ayala Pharmaceuticals, Inc.	8-K	001-39279	3.2	5/12/2020	
4.1	Amended and Restated Investors’ Rights Agreement	S-1/A	333-236942	4.1	5/4/2020	
4.2	Specimen Stock Certificate evidencing the shares of common stock	S-1/A	333-236942	4.2	5/4/2020	
4.3	Description of Securities					*
4.4	Form of Common Warrant	8-K	001-39279	4.1	2/22/2021	
4.5	Form of Pre-Funded Warrant	8-K	001-39279	4.2	2/22/2021	
4.6	Form of Indenture	S-3	333-256792	4.3	6/4/2021	
10.1#	Amended 2017 Stock Incentive Plan and form of agreements thereunder	S-1/A	333-236942	10.1	5/4/2020	
10.2#	Non-Employee Director Compensation Program	S-1/A	333-236942	10.2	5/4/2020	
10.3#	Form of Indemnification Agreement for Directors and Officers	S-1/A	333-236942	10.3	5/4/2020	
10.4	Lease Agreement, dated January 24, 2019, between Ayala-Oncology Israel Ltd. and Ogen Real Estate Maniv Ltd.	S-1	333-236942	10.4	3/6/2020	
10.5#	Employment Agreement, dated December 26, 2017, between Ayala-Oncology Israel Ltd. and Roni Mamluk, Ph.D., as amended	S-1	333-236942	10.5	3/6/2020	
10.6#	Employment Agreement, dated March 15, 2019, between Ayala-Oncology Israel Ltd. and Yossi Maimon, CPA, M.B.A., as amended	S-1	333-236942	10.6	3/6/2020	
10.7#	Employment Agreement, dated July 24, 2019, between the Registrant and Bristol-Myers Squibb Company, as amended	S-1	333-236942	10.7	5/4/2020	
10.8†	License Agreement, dated November 29, 2017, between the Registrant and Bristol-Myers Squibb Company, as amended	S-1/A	333-236942	10.8	5/4/2020	
10.9†	Evaluation, Option and License Agreement, dated December 19, 2018, between the Registrant and Novartis International Pharmaceutical Limited	S-1/A	333-236942	10.9	3/6/2020	

10.10	Securities Purchase Agreement, dated February 19, 2021, by and among Ayala Pharmaceuticals, Inc. and the Investors named therein.	8-K	001-39279	10.1	2/22/2021	
21.1	Subsidiaries of Ayala Pharmaceuticals, Inc.	S-1	333-236942	21.1	3/6/2020	
23.1	Consent of Independent Registered Public Accounting Firm					*
31.1	Certification of Principal Executive Officer Pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.					*
31.2	Certification of Principal Financial Officer Pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.					*
32.1	Certification of Principal Executive Officer Pursuant to 18 U.S.C. Section 1350, as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.					**
32.2	Certification of Principal Financial Officer Pursuant to 18 U.S.C. Section 1350, as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.					**
99.1	Resolutions adopted by the Board of Directors of the Registrant setting forth the information with respect to the Ratification required under Section 204 of the Delaware General Corporation Law					*
101.INS	Inline XBRL Instance Document—the instance document does not appear in the Interactive Data File because its XBRL tags are embedded within the Inline XBRL document					*
101.SCH	Inline XBRL Taxonomy Extension Schema Document					*
101.CAL	Inline XBRL Taxonomy Extension Calculation Linkbase Document					*
101.DEF	Inline XBRL Taxonomy Extension Definition Linkbase Document					*
101.LAB	Inline XBRL Taxonomy Extension Label Linkbase Document					*
101.PRE	Inline XBRL Taxonomy Extension Presentation Linkbase Document					*
104	Cover Page Interactive Data File (formatted as Inline XBRL and contained in Exhibit 101)					*

* Filed herewith.
** Furnished herewith.
# Indicates management contract or compensatory plan.
† Portions of this exhibit have been redacted in compliance with Regulation S-K Item 601(b)(10)(iv).

Item 16. Form 10-K Summary

None.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, as amended, the Registrant has duly caused this Report to be signed on its behalf by the undersigned, thereunto duly authorized**.**

Ayala Pharmaceuticals, Inc.

Date: March 28, 2022 By: /s/ Roni Mamluk, Ph.D.
Roni Mamluk, Ph.D.
Chief Executive Officer and President

Date: March 28, 2022 By: /s/ Yossi Maimon, CPA, M.B.A.
Yossi Maimon, CPA, M.B.A.
Chief Financial Officer

Pursuant to the requirements of the Securities Exchange Act of 1934, as amended, this Report has been signed below by the following persons on behalf of the Registrant in the capacities and on the dates indicated.

Name	Title	Date
/s/ Roni Mamluk, Ph.D. **Roni Mamluk, Ph.D.**	Chief Executive Officer, President and Director *(principal executive officer)*	March 28, 2022
/s/ Yossi Maimon, CPA, M.B.A. **Yossi Maimon, CPA, M.B.A.**	Chief Financial Officer *(principal financial and accounting officer)*	March 28, 2022
/s/ David Sidransky, M.D. **David Sidransky, M.D.**	Chairman of the Board of Directors	March 28, 2022
/s/ Robert Spiegel, M.D., F.A.C.P. **Robert Spiegel, M.D., F.A.C.P.**	Director	March 28, 2022
/s/ Murray A. Goldberg **Murray A. Goldberg**	Director	March 28, 2022
/s/ Vered Bisker-Leib, Ph.D., M.B.A. **Vered Bisker-Leib, Ph.D., M.B.A.**	Director	March 28, 2022

Exhibit 4.3

DESCRIPTION OF THE REGISTRANT'S SECURITIES REGISTERED PURSUANT TO SECTION 12 OF THE SECURITIES EXCHANGE ACT OF 1934, AS AMENDED

As of December 31, 2021, Ayala Pharmaceuticals, Inc. had one class of securities registered under Section 12 of the Securities Exchange Act of 1934, as amended (the "Exchange Act"). References herein to "we," "us," "our" and the "Company" refer to Ayala Pharmaceuticals, Inc. and not to any of its subsidiaries.

General

The following description summarizes some of the terms of our restated certificate of incorporation and restated bylaws, the amended and restated investors' rights agreement and of the General Corporation Law of the State of Delaware. Because it is only a summary, it does not contain all the information that may be important to you. For a complete description, you should refer to our restated certificate of incorporation, restated bylaws and the amended and restated investors' rights agreement, copies of which have been filed with the Securities and Exchange Commission, as well as the relevant provisions of the General Corporation Law of the State of Delaware.

Our authorized capital stock consists of 200,000,000 shares of common stock, par value $0.01 per share, and 10,000,000 shares of preferred stock, par value $0.01 per share.

Common Stock

Holders of our common stock are entitled to one vote for each share held on all matters submitted to a vote of stockholders and do not have cumulative voting rights. An election of directors by our stockholders shall be determined by a plurality of the votes cast by the stockholders entitled to vote on the election. Subject to the supermajority votes for some matters, other matters shall be decided by the affirmative vote of our stockholders having a majority in voting power of the votes cast by the stockholders present or represented and voting on such matter. Our restated certificate of incorporation and restated bylaws also provide that our directors may be removed only for cause and only by the affirmative vote of the holders of at least two-thirds in voting power of the outstanding shares of capital stock entitled to vote thereon. In addition, the affirmative vote of the holders of at least two-thirds in voting power of the outstanding shares of capital stock entitled to vote thereon is required to amend or repeal, or to adopt any provision inconsistent with, several of the provisions of our restated certificate of incorporation. See below under "—Anti-Takeover Effects of Delaware Law and Our Certificate of Incorporation and Bylaws—Amendment of Charter Provisions." Holders of common stock are entitled to receive proportionately any dividends as may be declared by our board of directors, subject to any preferential dividend rights of any series of preferred stock that we may designate and issue in the future.

In the event of our liquidation or dissolution, the holders of common stock are entitled to receive proportionately our net assets available for distribution to stockholders after the payment of all debts and other liabilities and subject to the prior rights of any outstanding preferred stock. Holders of common stock have no preemptive, subscription, redemption or conversion rights. Our outstanding shares of common stock are validly issued, fully paid and nonassessable. The rights, preferences and privileges of holders of common stock are subject to and may be adversely affected by the rights of the holders of shares of any series of preferred stock that we may designate and issue in the future.

Preferred Stock

Under the terms of our restated certificate of incorporation, our board of directors is authorized to direct us to issue shares of preferred stock in one or more series without stockholder approval. Our board of directors has the discretion to determine the rights, preferences, privileges and restrictions, including voting rights, dividend rights, conversion rights, redemption privileges and liquidation preferences, of each series of preferred stock.

The purpose of authorizing our board of directors to issue preferred stock and determine its rights and preferences is to eliminate delays associated with a stockholder vote on specific issuances. The issuance of preferred stock, while providing flexibility in connection with possible acquisitions, future financings and other corporate purposes, could have the effect of making it more difficult for a third party to acquire, or could discourage a third party from seeking to acquire, a majority of our outstanding voting stock. There are no shares of preferred stock outstanding, and we have no present plans to issue any shares of preferred stock.

Registration Rights

Certain of our stockholders are entitled to certain rights with respect to the registration of such shares for public resale under the Securities Act, pursuant to an amended and restated investors' rights agreement by and among us and certain of our stockholders, until the rights otherwise terminate pursuant to the terms of the investors' rights agreement. Additionally, holders of warrants to purchase our common stock are entitled to certain rights with respect to the registration for public resale under the Securities Act of shares of our common stock issued or issuable upon exercise of such warrants, pursuant to a securities purchase agreement by and among certain purchasers named therein. The registration of shares of common stock as a result of the following rights being exercised would enable holders to trade these shares without restriction under the Securities Act when the applicable registration statement is declared effective.

Piggyback Registration Rights

If we propose to register any shares of our common stock under the Securities Act, subject to certain exceptions, the holders of registrable securities will be entitled to notice of the registration and to include their shares of registrable securities in the registration. If our proposed registration involves an underwriting, the managing underwriter of such offering will have the right to limit the number of shares to be underwritten for reasons related to the marketing of the shares.

Form S-3 Registration Rights

If, at any time after we become entitled under the Securities Act to register our shares on a registration statement on Form S-3, the holders of at least 20% of the registrable securities then outstanding request in writing that we effect a registration with respect to all or part of such registrable securities then outstanding and having an anticipated aggregate offering amount, net of expenses, of at least $3,000,000, we will be required to effect such registration.

Private Placement Form S-3 Registration Rights

We have also agreed to use reasonable best efforts to register certain shares of our common stock issued, or issuable upon exercise of certain warrants, for public resale pursuant to the Securities Act on a registration statement on Form S-3 promptly following the date such form is available for use by us, but in no event later than June 15, 2021. On June 6, 2021, we registered such shares on a registration statement on Form S-3 (File No. 333-256793).

Expenses and Indemnification

Ordinarily, other than underwriting discounts and commissions, we will be required to pay all expenses incurred by us related to any registration effected pursuant to the exercise of these registration rights. These expenses may include all registration and filing fees, printing expenses, fees and disbursements of our counsel, reasonable fees and disbursements of a counsel for the selling securityholders and blue sky fees and expenses. Additionally, we have agreed to indemnify selling stockholders for damages, and any legal or other expenses reasonably incurred, arising from or based upon any untrue statement of a material fact contained in any registration statement, an omission or alleged omission to state a material fact in any registration statement or necessary to make the statements therein not misleading, or any violation or alleged violation by the indemnifying party of securities laws, subject to certain exceptions.

Termination of Registration Rights

The registration rights terminate upon the earlier of the date that is five years after the closing of our initial public offering, such time as Rule 144 or another similar exemption under the Securities Act is available for the sale of all of such holders' shares without limitation during a three-month period without registration and the closing of a deemed liquidation event, as defined in the investors' rights agreement.

Anti-Takeover Effects of Delaware Law and Our Certificate of Incorporation and Bylaws

Some provisions of Delaware law, our restated certificate of incorporation and our restated bylaws could make the following transactions more difficult: an acquisition of us by means of a tender offer; an acquisition of us by means of a proxy contest or otherwise; or the removal of our incumbent officers and directors. It is possible that these provisions could make it more difficult to accomplish or could deter transactions that stockholders may otherwise consider to be in their best interest or in our best interests, including transactions which provide for payment of a premium over the market price for our shares.

These provisions, summarized below, are intended to discourage coercive takeover practices and inadequate takeover bids. These provisions are also designed to encourage persons seeking to acquire control of us to first negotiate with our board of directors. We believe that the benefits of the increased protection of our potential ability to negotiate with the proponent of an unfriendly or unsolicited proposal to acquire or restructure us outweigh the disadvantages of discouraging these proposals because negotiation of these proposals could result in an improvement of their terms.

Undesignated Preferred Stock

The ability of our board of directors, without action by the stockholders, to issue up to 10,000,000 shares of undesignated preferred stock with voting or other rights or preferences as designated by our board of directors could impede the success of any attempt to change control of us. These and other provisions may have the effect of deferring hostile takeovers or delaying changes in control or management of our company.

Stockholder Meetings

Our restated certificate of incorporation and restated bylaws provide that a special meeting of stockholders may be called only by our chairman of the board, chief executive officer or president (in the absence of a chief executive officer), or by a resolution adopted by a majority of our board of directors.

Requirements for Advance Notification of Stockholder Nominations and Proposals

Our restated bylaws establish advance notice procedures with respect to stockholder proposals to be brought before a stockholder meeting and the nomination of candidates for election as directors, other than nominations made by or at the direction of the board of directors or a committee of the board of directors.

Elimination of Stockholder Action by Written Consent

Our restated certificate of incorporation eliminates the right of stockholders to act by written consent without a meeting.

Staggered Board

Our board of directors is divided into three classes. The directors in each class serve for a three-year term, one class being elected each year by our stockholders. This system of electing and removing directors may tend to discourage a third party from making a tender offer or otherwise attempting to obtain control of us, because it generally makes it more difficult for stockholders to replace a majority of the directors.

Removal of Directors

Our restated certificate of incorporation provides that no member of our board of directors may be removed from office by our stockholders except for cause and, in addition to any other vote required by law, upon the approval of the holders of at least two-thirds in voting power of the outstanding shares of stock entitled to vote in the election of directors.

Stockholders Not Entitled to Cumulative Voting

Our restated certificate of incorporation does not permit stockholders to cumulate their votes in the election of directors. Accordingly, the holders of a majority of the outstanding shares of our common stock entitled to vote in any election of directors can elect all of the directors standing for election, if they choose, other than any directors that holders of our preferred stock may be entitled to elect.

Delaware Anti-Takeover Statute

We are subject to Section 203 of the General Corporation Law of the State of Delaware, which prohibits persons deemed to be "interested stockholders" from engaging in a "business combination" with a publicly held Delaware corporation for three years following the date these persons become interested stockholders unless the business combination is, or the transaction in which the person became an interested stockholder was, approved in a prescribed manner or another prescribed exception applies. Generally, an "interested stockholder" is a person who, together with affiliates and associates, owns, or within three years prior to the determination of interested stockholder status did own, 15% or more of a corporation's voting stock. Generally, a "business combination" includes a merger, asset or stock sale, or other transaction resulting in a financial benefit to the interested stockholder. The existence of this provision may have an anti-takeover effect with respect to transactions not approved in advance by the board of directors.

Choice of Forum

Our restated certificate of incorporation provides that, unless we consent in writing to the selection of an alternative form, the Court of Chancery of the State of Delaware will be the sole and exclusive forum for: (1) any derivative action or proceeding brought on our behalf; (2) any action asserting a claim of breach of a fiduciary duty or other wrongdoing by any of our directors, officers, employees or agents to us or our stockholders; (3) any action asserting a claim against us arising pursuant to any provision of the General Corporation Law of the State of Delaware or our certificate of incorporation or bylaws; (4) any action to interpret, apply, enforce or determine the validity of our certificate of incorporation or bylaws; or (5) any action asserting a claim governed by the internal affairs doctrine. Under our restated certificate of incorporation, this exclusive forum provision will not apply to claims which are vested in the exclusive jurisdiction of a court or forum other than the Court of Chancery of the State of Delaware, or for which the Court of Chancery of the State of Delaware does not have subject matter jurisdiction. For instance, the provision would not apply to actions arising under federal securities laws, including suits brought to enforce any liability or duty created by the Securities Act, Exchange Act, or the rules and regulations thereunder. Our restated certificate of incorporation further provides that, unless we consent in writing to the selection of an alternative forum, the federal district courts of the United States of America shall, to the fullest extent permitted by law, be the sole and exclusive forum for the resolution of any complaint asserting a cause of action arising under the Securities Act. Our restated certificate of incorporation also provides that any person or entity purchasing or otherwise acquiring any interest in shares of our capital stock will be deemed to have notice of and to have consented to these choice of forum provisions. It is possible that a court of law could rule that either or both of the choice of forum provisions contained in our restated certificate of incorporation is inapplicable or unenforceable if it is challenged in a proceeding or otherwise.

Amendment of Charter Provisions

The amendment of any of the above provisions, except for the provision making it possible for our board of directors to issue preferred stock and the provision prohibiting cumulative voting, would require approval by holders of at least two-thirds in voting power of the outstanding shares of stock entitled to vote thereon.

The provisions of Delaware law, our restated certificate of incorporation and our restated bylaws could have the effect of discouraging others from attempting hostile takeovers and, as a consequence, they may also inhibit temporary fluctuations in the market price of our common stock that often result from actual or rumored hostile takeover attempts. These provisions may also have the effect of preventing changes in the composition of our board and management. It is possible that these provisions could make it more difficult to accomplish transactions that stockholders may otherwise deem to be in their best interests.

Stock Exchange Listing

Our common stock is listed on The Nasdaq Global Market under the symbol "AYLA."

Exhibit 23.1

Consent of Independent Registered Public Accounting Firm

We consent to the incorporation by reference in the Registration Statement (Form S-3) of Ayala Pharmaceuticals, Inc. and in the related Prospectus of our report dated March 28, 2022 (which contains an explanatory paragraph describing conditions that raise substantial doubt about the Company's ability to continue as a going concern as described in Note 1 to the consolidated financial statements), with respect to the consolidated financial statements of Ayala Pharmaceuticals, Inc. , included in this Annual Report (Form 10-K) for the year ended December 31, 2021.

Tel-Aviv, Israel
March 28, 2022

/s/ Kost, Forer, Gabbay & Kasierer
KOST, FORER, GABBAY & KASIERER

A Member of EY Global

Exhibit 31.1

CERTIFICATION

I, Roni Mamluk, certify that:

1. I have reviewed this Annual on Form 10-K of Ayala Pharmaceuticals, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

   (a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   (b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, 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;

   (c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   (d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

   (a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   (b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 28, 2022

By: /s/ Roni Mamluk

Roni Mamluk, Ph.D.
Chief Executive Officer
(principal executive officer)

Exhibit 31.2

CERTIFICATION

I, Yossi Maimon, certify that:

1. I have reviewed this Annual Report on Form 10-K of Ayala Pharmaceuticals, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

   (a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   (b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, 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;

   (c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   (d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

   (a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   (b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 28, 2022

By: /s/ Yossi Maimon

Yossi Maimon, CPA, M.B.A.
Chief Financial Officer
(principal financial officer)

Exhibit 32.1

CERTIFICATION PURSUANT TO
18 U.S.C. SECTION 1350, AS ADOPTED PURSUANT TO
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

In connection with the Annual Report on Form 10-K of Ayala Pharmaceuticals, Inc. (the "Company") for the period ended December 31, 2021 as filed with the Securities and Exchange Commission on the date hereof (the "Report"), I certify, pursuant to 18 U.S.C. § 1350, as adopted pursuant to § 906 of the Sarbanes-Oxley Act of 2002, that:

(1) The Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934, as amended; and

(2) The information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Date: March 28, 2022

By: /s/ Roni Mamluk

Roni Mamluk, Ph.D.
President and Chief Executive Officer
(principal executive officer)

Exhibit 32.2

CERTIFICATION PURSUANT TO
18 U.S.C. SECTION 1350, AS ADOPTED PURSUANT TO
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

In connection with the Annual Report on Form 10-K of Ayala Pharmaceuticals, Inc. (the "Company") for the period ended December 31, 2021 as filed with the Securities and Exchange Commission on the date hereof (the "Report"), I certify, pursuant to 18 U.S.C. § 1350, as adopted pursuant to § 906 of the Sarbanes-Oxley Act of 2002, that:

(1) The Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934, as amended; and

(2) The information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Date: March 28, 2022

By: /s/ Yossi Maimon

Yossi Maimon, CPA, M.B.A.
Chief Financial Officer
(principal financial officer)

Exhibit 99.1

AYALA PHARMACEUTICALS, INC.

UNANIMOUS WRITTEN CONSENT OF THE BOARD OF DIRECTORS

The undersigned, being all of the members of the Board of Directors (the "***Board***") of Ayala Pharmaceuticals, Inc., a Delaware corporation (the "***Company***"), acting in accordance with Section 141(f) of the General Corporation Law of the State of Delaware (the "***General Corporation Law***"), hereby take the following actions and adopt the following recitals and resolutions by unanimous written consent in lieu of a meeting:

Ratification of Defective Acts

WHEREAS, on October 5, 2021, the Company purported to issue 249,700 shares of the Company's Common Stock, par value $0.01 per share, in one or more "at-the-market" offerings pursuant to the Company's Registration Statement on Form S-3 (File No. 333-256792) (the "***ATM Offerings***") through Jefferies LLC acting as sales agent (the "***Stock Issuance***");

WHEREAS, pursuant to resolutions adopted by the Board on May 13, 2021, the Board delegated to the ATM Pricing Committee of the Board (the "***ATM Pricing Committee***") the full power, authority and discretion on behalf of the Board with regard to the ATM Offerings;

WHEREAS, the Board has determined that the Stock Issuance may constitute a defective corporate act and the shares issued in connection therewith may constitute putative stock (as defined in Section 204(h) of the General Corporation Law) because the authority to consummate the Stock Issuance approved by the ATM Pricing Committee expired on September 30, 2021 and the Stock Issuance failed to have been duly authorized by the Board in accordance with Section 152 of the General Corporation Law; and

WHEREAS, the Board has determined that it is advisable and in the best interests of the Company and its stockholders to ratify the Stock Issuance and the issuance of putative stock related thereto pursuant to and in accordance with Section 204 of the General Corporation Law.

NOW, THEREFORE, BE IT RESOLVED, that the Stock Issuance is the defective corporate act to be ratified hereby.

RESOLVED FURTHER, that the date of the Stock Issuance is October 5, 2021.

RESOLVED FURTHER, that the Stock Issuance involved the issuance of 249,700 shares of Common Stock on October 5, 2021, all of which were putative stock (the "***Putative Stock***").

RESOLVED FURTHER, that the nature of the failure of authorization in respect of the Stock Issuance is the failure of such issuance to have been duly authorized by the Board in accordance with Section 152 of the General Corporation Law.

RESOLVED FURTHER, that, pursuant to and in accordance with Section 204 of the General Corporation Law, the ratification of the Stock Issuance and the issuance of the Putative Stock be, and hereby is, approved, adopted and confirmed in all respects.

WHEREAS, any claim that any defective corporate act or putative stock referenced herein being ratified under Section 204 of the General Corporation Law is void or voidable due to the failure(s) of authorization, or that the Delaware Court of Chancery should declare in its discretion that the ratification thereof in accordance with Section 204 of the General Corporation Law not be effective or be effective only on certain conditions must be brought within the later of 120 days from the relevant validation effective time and the time at which the notice, if any, required by Section 204(g) is given.

NOW, THEREFORE, BE IT RESOLVED, that the officers of the Company be, and each of them hereby is, authorized, empowered and directed, for and on behalf of the Company, to deliver a notice of the ratification of the defective corporate act and putative stock set forth herein in the form and containing the information required by Section 204 of the General Corporation Law.

RESOLVED FURTHER, that the officers of the Company be, and each of them hereby is, authorized, empowered and directed, for and on behalf of the Company, to take any and all actions, to negotiate for and enter into agreements and amendments to agreements, to perform all such acts and things, to execute, file, deliver or record in the name and on behalf of the Company, all such certificates, instruments, agreements or other documents, and to make all such payments as they, in their judgment, or in the judgment of any one or more of them, may deem necessary, advisable or appropriate in order to carry out the purpose and intent of, or consummate the transactions contemplated by the foregoing resolutions and/or all of the transactions contemplated therein or thereby, the authorization therefor to be conclusively evidenced by the taking of such action or the execution and delivery of such certificates, instruments, agreements or documents.

This Unanimous Written Consent may be executed in counterparts, including by facsimile, PDF, email or any electronic signature complying with the U.S. federal ESIGN Act of 2000 (*e.g.*, www.docusign.com), each of which shall be deemed an original and all of which together shall constitute one and the same instrument. This Unanimous Written Consent shall be filed with the minutes of the proceedings of the Board.

[*Signature Page Follows*]

IN WITNESS WHEREOF, the undersigned, being all of the members of the Board, do hereby execute this Unanimous Written Consent on the date set forth opposite each such undersigned's name.

Dated: November 29, 2021

/s/ Vered Bisker-Leib, Ph.D.
Vered Bisker-Leib, Ph.D.

Dated: November 29, 2021

/s/ Murray Goldberg
Murray Goldberg

Dated: November 30, 2021

/s/ Roni Mamluk, Ph.D.
Roni Mamluk, Ph.D.

Dated: November 30, 2021

/s/ David Sidransky, M.D.
David Sidransky, M.D.

Dated: November 29, 2021

/s/ Robert Spiegel, M.D., F.A.C.P.
Robert Spiegel, M.D., F.A.C.P.