UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 10-K

☒ **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 001-40215

Instil Bio, Inc.

(Exact name of registrant as specified in its charter)

Delaware	**83-2072195**
(State or other jurisdiction of incorporation or organization)	(I.R.S. Employer Identification No.)
3963 Maple Avenue, Suite 350 **Dallas, Texas**	**75219**
(Address of Principal Executive Offices)	(Zip Code)

(972) 499-3350
Registrant's telephone number, including area code
Not Applicable
(Former name, former address and former fiscal year, if changed since last report)

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, $0.000001 par value per share	TIL	The Nasdaq Stock Market LLC

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

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

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

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate web site, if any, 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 files). Yes ☒ No ☐

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

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 7(a)(2)(B) of the Securities 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 ☒

As of June 30, 2021, the last business day of the registrant’s most recently completed second fiscal quarter, the aggregate market value of the registrant’s common stock held by non-affiliates of the registrant was approximately $1,070.6 million, based on the closing price of the registrant’s common stock on the Nasdaq Global Select Market on June 30, 2021 of $19.32 per share.

Indicate the number of shares outstanding of each of the issuer’s classes of common stock, as of the latest practicable date:

Class of Common Stock	Outstanding at
129,129,995 shares of Common Stock, $0.000001 par value per share	March 3, 2022

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant’s definitive proxy statement to be filed with the Securities and Exchange Commission (SEC) subsequent to the date hereof pursuant to Regulation 14A in connection with the registrant's 2022 Annual Meeting of Stockholders, are incorporated by reference into Part III of this Annual Report on Form 10-K. Such proxy statement will be filed with the SEC not later than 120 days after the conclusion of the registrant's fiscal year ended December 31, 2021.

TABLE OF CONTENTS

	Page
Part I	
Item 1. Business	2
Item 1A. Risk Factors	39
Item 1B. Unresolved Staff Comments	101
Item 2. Properties	101
Item 3. Legal Proceedings	101
Item 4. Mine Safety Disclosures	101
Part II	
Item 5. Market for Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities	102
Item 6. Reserved	103
Item 7. Management's Discussion and Analysis of Financial Condition and Results of Operations	104
Item 7A. Quantitative and Qualitative Disclosures About Market Risk	114
Item 8. Financial Statements and Supplementary Data	115
Item 9. Changes In and Disagreement With Accountants on Accounting and Financial Disclosure	143
Item 9A. Controls and Procedures	143
Item 9B. Other Information	144
Item 9C. Disclosure Regarding Foreign Jurisdictions that Prevent Inspections	144
Part III	
Item 10. Directors, Executive Officers and Corporate Governance	145
Item 11. Executive Compensation	145
Item 12. Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters	145
Item 13. Certain Relationships and Related Transactions, and Director Independence	145
Item 14. Principal Accounting Fees and Services	145
Part IV	
Item 15. Exhibits, Financial Statement Schedules	146
Item 16. Form 10-K Summary	147
Signatures	148

Part I

Item 1. Business.

Overview

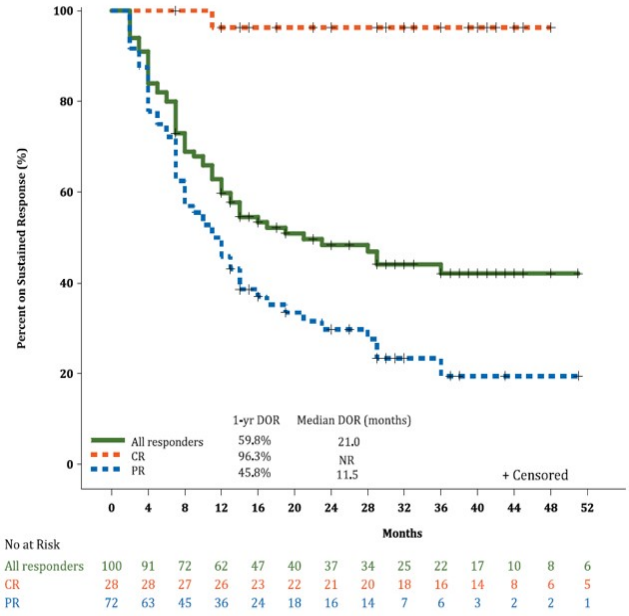
We are a clinical-stage biopharmaceutical company focused on developing an innovative cell therapy pipeline of autologous tumor infiltrating lymphocyte, or TIL, therapies for the treatment of patients with cancer. We have assembled an accomplished team with a successful track record in the development, manufacture, regulatory approval and commercialization of multiple cell therapies. Using our optimized and scalable manufacturing process, we are advancing our lead TIL product candidate, ITIL-168, for the treatment of advanced melanoma. Based on the clinical results from a compassionate use program with a TIL product that was manufactured using a prior version of the ITIL-168 manufacturing process, we submitted an investigational new drug application, or IND, to the U.S. Food and Drug Administration, or the FDA, and were authorized to initiate a Phase 2 trial in late 2021 with expected topline safety and efficacy data in 2023, which we believe could support a biologics license application, or BLA submission. We plan to initiate a Phase-1 trial of ITIL-168 in additional indications with unmet medical need, including cutaneous squamous cell carcinoma, or CSCC, non-small cell lung cancer, or NSCLC, head and neck squamous cell carcinoma, or HNSCC, and cervical cancer, in 2022. ITIL-168 will be manufactured in our company-operated in-house manufacturing facilities for both our clinical trials and commercial sales, if approved.

We are also developing a novel class of genetically engineered TIL therapies using our Co-Stimulatory Antigen Receptor, or CoStAR, platform. These modified TILs still rely on their native, patient-specific T cell receptors, or TCRs, to bind to tumor neoantigens, but have been enhanced to express novel CoStAR molecules, which bind to shared tumor-associated antigens and provide potent costimulation to T cells within the tumor microenvironment. We believe that the ability of CoStAR to augment the activation of TILs upon native TCR-mediated recognition of tumor neoantigens has the potential to bring TIL therapy to patients with cancer types that have been historically resistant to immunotherapy. We anticipate filing an investigational new drug, or IND, application for our lead CoStAR-TIL product candidate, ITIL-306, in 2022.

We believe the critical advantage of TIL therapy over other cell therapies relates to the intrinsic and diverse anti-tumor reactivity of TILs. Unlike most cell therapies in development for solid tumors, which only recognize a single target antigen shared across a diverse patient population, TILs are polyclonal and therefore have the ability to recognize the broad set of antigens unique to each patient. This comprehensive polyclonality helps overcome a major limitation of cell therapies, such as CAR-Ts and TCR-Ts, by providing the requisite diversity to match the marked heterogeneity of solid tumors.

The successful use of TIL therapy to treat solid tumors was first published in 1988 by Steven A. Rosenberg, M.D., Ph.D., and his colleagues from the National Cancer Institute, or NCI, who demonstrated remissions in patients with advanced melanoma who had been treated with TILs. Since these initial reports, clinical studies of TILs have expanded significantly. In a study published in *Annals of Oncology* in 2019, U. Dafni and colleagues conducted a meta-analysis of clinical trials of TIL therapies published between 1988 and 2016, which reported an overall remission rate, or ORR, of 41% and a complete remission, or CR, rate of 12% in 410 heavily pretreated patients with metastatic melanoma. As shown below, in patients for whom detailed follow-up was available, the CRs were found to be remarkably durable, with only one of 28 patients experiencing disease recurrence.

TIL Therapy Demonstrated Durable CRs
in Patients with Melanoma in Clinical Trials Between 1988 and 2016



In addition to melanoma, TIL therapy has also demonstrated efficacy in multiple other solid tumors, including NSCLC, HNSCC, and cervical cancer. However, despite these compelling clinical results, TIL therapy has largely been limited to the academic or compassionate use settings due to the lack of an industrialized and scalable process for the manufacture of these products.

By leveraging our team's experience, we are executing on our plan to efficiently launch in-house capabilities of manufacturing, process development, clinical operations, regulatory strategy and research and development. We have created a robust, reproducible process to generate well-characterized and commercially viable TIL product candidates that we believe will provide patients with long-term therapeutic benefit.

Our Strengths

Our goal is to become the leader in the design, manufacture and delivery of TIL therapies to patients with cancer. We believe the following strengths will enable us to achieve this goal:

Highly experienced team. Our senior management team and a large fraction of our operational staff have extensive experience in cell therapy, with many having participated in the design and execution of the clinical development, manufacture and regulatory approval of Yescarta and Tecartus at Kite Pharma/Gilead, as well as the development of other clinical-stage cell therapy product candidates. In addition, our team and scientific advisors have a track record of successfully leading the technology discovery, process development, GMP manufacturing and clinical operations functions at other cell therapy companies.

Robust clinical development experience with TILs. Members of our team have been generating and improving TIL therapy for over a decade, and a TIL product manufactured by us has been used in the treatment of patients with refractory melanoma through a compassionate use program at the Christie Hospital in Manchester, United Kingdom,

which is the largest single-site cancer center in Europe. In the 21 patients treated through the compassionate use program using a TIL product that was manufactured using a prior version of the ITIL-168 manufacturing process, we observed a CR in four patients (19%) and a partial remission, or PR, in 10 patients (48%), resulting in an ORR of 67%. In addition, four patients reported SD, resulting in a disease control rate, or DCR, of 86%. Ten of the 21 patients have died from complications arising from disease progression. The results from the compassionate use program do not provide a guarantee that ITIL-168 will be deemed to be safe or effective for the treatment of melanoma or additional indications, and extensive clinical testing and regulatory approval will be required before ITIL-168 can be commercially marketed for the treatment of melanoma. Based on these results, together with our development and manufacturing expertise, we intend to transform TIL therapy into what we believe will be a scalable, convenient and effective option for patients with cancer.

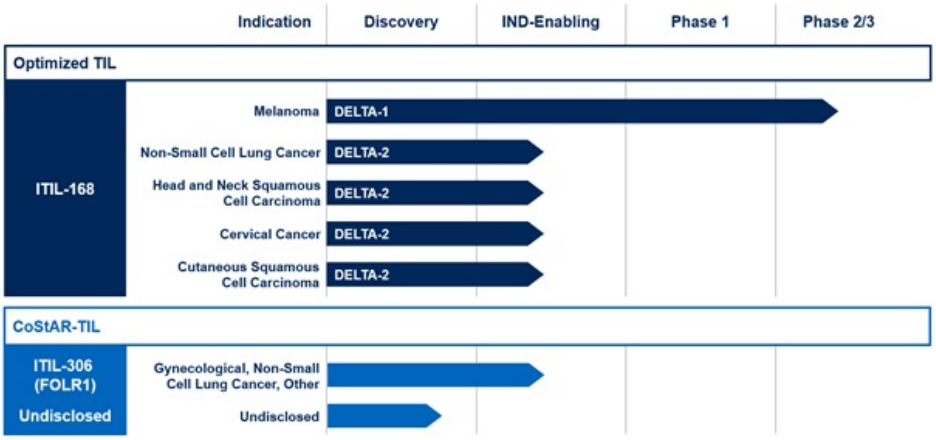
Optimized and scalable manufacturing process. We have developed a manufacturing process customized for autologous TIL therapies to maximize manufacturing success rate and potential for clinical efficacy beyond current practices. To ensure product quality and consistency, we have chosen to maintain full control of the entire manufacturing process, from the procurement of tumor samples through the shipping of the final product, without any outsourcing of core manufacturing process or quality control testing steps. Our process includes the optimized cryopreservation of both the digested tumor at the beginning to preserve cell viability and potency and the final product at the end to provide increased shelf life. Importantly, our cryopreservation process also provides significant scheduling flexibility for physicians and patients.

Company-operated in-house manufacturing facilities. We believe we are well positioned to execute on our clinical development plans and serve the U.S. and European markets with our existing and planned infrastructure. We have invested and plan to continue to invest in our manufacturing capabilities on two continents, with one facility in the United States in Tarzana, California for both clinical and commercial manufacturing and another in Manchester, United Kingdom for clinical manufacturing. By controlling and operating our manufacturing facilities on two continents, we believe we have the unique ability to more efficiently implement continuous improvements into our operations and to readily provide therapies to patients across a broad geography. With planned capacity across both of our facilities, we expect to have sufficient doses for all our clinical trials, as well as to meet the initial commercial demand of ITIL-168, if approved.

Strong capitalization. Since 2019, we have financed our operations with $719.0 million in net proceeds raised in our initial public offering and private placements of convertible preferred stock to date. This funding has enabled us to assemble a team with experience across the entire spectrum of cell therapy development, including clinical development and operations, regulatory submissions, process engineering, quality analytics, manufacturing and strategic commercialization planning.

Our Pipeline

We are building an innovative pipeline of optimized TIL product candidates, including both unmodified and genetically engineered TILs, for the treatment of patients with cancer. We own worldwide rights to all our product candidates. Our current pipeline is summarized in the diagram below.



Our lead product candidate, ITIL-168, is an autologous TIL therapy that we are initially developing for the treatment of PD-1-inhibitor relapsed or refractory advanced melanoma. We are utilizing an optimized and scalable manufacturing process that we believe will differentiate the profile of ITIL-168 from other cell therapies, including other TIL therapies. Our process for ITIL-168 manufacturing begins with the complete digestion of the tumor tissue, which releases all TILs from the tumor microenvironment and enables cryopreservation of the digested tumor at the beginning of the process to preserve cell viability and potency. Additionally, we cryopreserve the final product to provide increased shelf life. Our cryopreservation process at both the beginning and end of the manufacturing process provides significant scheduling flexibility for physicians and patients.

We have generated preliminary safety and efficacy data in advanced melanoma in the context of a compassionate use program in the United Kingdom, using a TIL product that was produced with a prior version of the ITIL-168 manufacturing process. Twenty-one patients with stage IV metastatic cutaneous melanoma were treated in this compassionate use program between 2011 and 2019. Treatment led to an ORR of 67%, including four patients (19%) who achieved CR and ten patients (48%) who achieved a PR. The DCR, which included patients with CR, PR or SD, was 86%. Based on these clinical results and our discussions with the FDA, we submitted IND for ITIL-168 and were authorized to initiate a Phase 2 trial in late 2021 with expected topline safety and efficacy data in 2023, which we believe could support a BLA submission. Additionally, in 2022, we intend to initiate Phase 1 trials of ITIL-168 in tumor types where evidence of immune cell recognition and elimination of cancer cells has been observed, such as CSCC, NSCLC, HNSCC and cervical cancer.

We are also developing genetically engineered TIL product candidates modified with CoStAR to augment the activation of TILs in the tumor microenvironment. In preclinical studies, CoStAR+ T cells demonstrated markedly increased activity as compared to normal T cells, including enhanced cytokine expression and proliferative capacity. CoStAR's modular architecture can be adapted to potentially target any cell surface antigen, which will allow us to develop additional CoStAR-TIL product candidates that enhance TIL function in multiple solid tumors.

Our lead CoStAR-TIL product candidate, ITIL-306, expresses a CoStAR molecule designed to recognize folate receptor alpha, or FOLR1, a tumor-associated antigen that is expressed on numerous solid tumors, including ovarian cancer, uterine cancer, NSCLC and renal cancer. We believe that ITIL-306 has the potential to increase anti-tumor activity due to its ability to improve proliferation and enhance cytokine secretion while retaining the specificity and polyclonality of TILs. We intend to submit an IND for ITIL-306 in 2022 and initiate a Phase 1 trial in 2022 to evaluate safety, feasibility and preliminary efficacy in multiple tumor types.

The modular nature of our CoStAR platform allows for multiple product candidates to be developed with minimal changes to the fundamental architecture of the molecule. We have generated a number of constructs containing antigen-binding domains directed against different tumor-associated antigens that are expressed by a

wide variety of tumor types, including stomach, colorectal, pancreatic, breast and other cancers. We intend to select our next CoStAR-TIL product candidate for IND-enabling studies in 2022.

Our History and Team

We were founded in August 2018, and in early 2019, we in-licensed our foundational TIL technology from Immetacyte Ltd. and subsequently raised our Series A round of funding from Curative Ventures. In March 2020, we acquired Immetacyte Ltd., which had been manufacturing a TIL product for the compassionate use program at the Christie Hospital in the United Kingdom from 2011 to 2019. Since 2019, we have financed our operations with $719.0 million in net proceeds raised in our initial public offering and private placements of convertible preferred stock to date.

We have assembled a team of industry veterans with deep experience in conducting all phases of development, from early stage clinical trials through regulatory approval across multiple regions, as well as in the commercial manufacture and marketing of cell therapies. Our management team consists of entrepreneurs, physicians and scientists with prior experience at cell therapy and oncology companies such as Kite Pharma/Gilead, Amgen, Pfizer, Genentech and Johnson & Johnson, among others.

Our Strategy

Our goal is to leverage our optimized and scalable manufacturing process to deliver innovative, life-saving TIL therapies to patients with cancer. In order to achieve this goal, our strategy involves the following key elements:

- **Develop and commercialize ITIL-168 in advanced melanoma.** We filed an IND and initiated a Phase 2 trial of ITIL-168 in patients with relapsed or refractory advanced melanoma in late 2021. Based on our discussions with the FDA and the clinical results generated through a compassionate use program with a TIL product that was manufactured using a prior version of the ITIL-168 manufacturing process, our Phase 2 trial was designed to support a BLA submission. We believe that our optimized and scalable manufacturing process for TIL therapies, coupled with our team's prior experience and success with developing and obtaining regulatory approval for multiple complex autologous cell therapies, will enable us to efficiently advance the development, manufacture and regulatory approval of ITIL-168.
- **Expand ITIL-168 into multiple solid tumors beyond melanoma.** In addition to melanoma, we intend to develop ITIL-168 in tumor types where evidence of immune cell recognition and elimination of cancer cells has been observed, such as CSCC, NSCLC, HNSCC and cervical cancer. In 2022 we plan to initiate a Phase 1 trial in patients with NSCLC, HNSCC, and cervical cancer, and CSCC, tumor types where clinical proof of concept has been established for TIL therapy and/or PD-1 blockade.
- **Leverage our experience with ITIL-168 to develop our CoStAR platform of engineered TIL therapies.** By enhancing the activity of TILs with our CoStAR molecules, we believe we will be able to demonstrate efficacy in tumor types that historically have been resistant to immunotherapy, including TILs. We have observed that TILs enhanced with CoStAR molecules demonstrated a markedly increased ability to respond to tumor cells *in vitro* as compared to normal T cells. Our preclinical studies have shown robust TCR- and CoStAR-dependent proliferation, as well as increased secretion of activating cytokines and decreased levels of immunosuppressive cytokines into the tumor microenvironment. By modulating the local immunological milieu, our CoStAR-TIL product candidates could recruit additional anti-tumor immune cells and reduce recruitment of suppressive cells. We leverage the optimized and scalable manufacturing process developed for ITIL-168 for our CoStAR-TIL product candidates, which will allow us to efficiently develop a portfolio of CoStAR-TIL pipeline candidates. We plan to assess the safety, feasibility and efficacy of CoStAR-TIL product candidates in several tumor types where TILs have not yet been systematically tested or response to TIL therapy has been poor. We intend to file an IND for our lead CoStAR-TIL product candidate, ITIL-306, in 2022.

- **Enhance and expand our global manufacturing capabilities and capacity.** We have invested and plan to continue to invest in our manufacturing capabilities on two continents, with one facility in the United States in Tarzana, California and another in Manchester, United Kingdom. Our clinical capacity is up to approximately 150 patient doses per year at our Manchester facility and is expected to expand to a capacity of up to approximately 500 patient doses per year from both of our facilities combined in 2022, which we believe will fully support the clinical development of our programs. With continued investments and buildout, we expect to have sufficient capacity to meet the initial commercial demand estimates for ITIL-168, if approved. While we believe we are well positioned to serve the U.S. and European markets with our existing and planned infrastructure, we intend to continue expanding our manufacturing network into additional regions, as needed.
- **Continuously improve and refine our manufacturing process and operations.** We plan to pursue process development efforts on two distinct but strategically aligned paths. The first path includes our continuous improvement initiatives, which are designed to allow us to implement rapid design iterations that incrementally improve process efficiency, robustness and control. The second path includes our longer-term manufacturing innovation initiatives, where we will drive towards generational and disruptive changes to our manufacturing methods. For example, we plan to introduce automated bioprocessing equipment and eliminate select reagents from the manufacturing process to achieve shorter manufacturing times and reduce costs. We believe these improvements will continually reduce manufacturing and operational costs while preserving product quality, allowing us to potentially make our TIL therapies globally accessible.

Background on TILs

Overview of Engineered T Cell Therapies

T cells are one of the key cell types of the immune system. Their roles include targeting cells that pose a threat to our health, such as infected or cancerous cells, for direct killing, as well as producing soluble mediators of immunity, like cytokines, to improve or otherwise modulate the overall immune response. T cells recognize and target these cells for killing through the engagement of the TCR by peptide antigens presented on the surface of the target cell by the major histocompatibility complex, or MHC. T cell therapies can be generated from peripheral blood collected and separated via leukapheresis to isolate T cells that are then genetically modified to express relevant TCRs or CARs. Alternatively, T cell therapies can be generated from tumor-infiltrating lymphocytes, or TILs, collected from a resected tumor.

CAR-T and TCR-T therapies are cell products composed of T cells that have been genetically engineered to recognize a specific cancer-related antigen on the surface of tumor cells. Recently, multiple CAR-T therapies such as Yescarta, Tecartus and Kymriah, which each target the B-cell antigen CD19, have achieved regulatory approval after demonstrating efficacy in the treatment of several kinds of B-cell malignancies. Despite these successes in blood cancers, CAR-T and TCR-T therapies have shown limited efficacy in the treatment of solid tumors. In addition to the general lack of anti-tumor activity, serious and potentially fatal toxicities commonly seen with these therapies have been observed in multiple clinical trials in solid tumors. These side effects include those related to normal tissue distribution of the target antigen, as well as antigen-independent toxicities such as cytokine release syndrome, neurotoxicity and prolonged pancytopenia. For these reasons, there are currently no approved CAR-T or TCR-T therapies for the treatment of solid tumors.

Tumor heterogeneity is a major obstacle in successfully treating solid tumors with single-antigen targeting modalities like CAR-Ts and TCR-Ts. Individual cancer cells within tumors are clonally diverse and thus display significant differences in the profile of antigens they express. As most CAR-T and TCR-T therapies are engineered to target a single antigen, they lack the ability to address the profound antigenic heterogeneity found within solid tumors. Patients with solid tumors who have been treated with these therapies are at increased risk of clonal escape, which is the growth of tumor cells that do not express the antigen targeted by the therapy. Clonal escape, also known as target-negative relapse, is a well-described mechanism by which single antigen targeting therapies fail in the treatment of cancer.

Other limitations of both CAR-T and TCR-T therapies are related to tissue distribution of the target antigen itself. CAR-T cells target cell surface proteins that are often found on both normal tissues and tumors, leading to on-target, off-tumor toxicity. In the case of anti-CD19 CAR-T cell products, the complete elimination of normal B cells is an expected side effect and results in possibly permanent immunosuppression. Also, because CAR-T therapies can only target surface antigens, they are not able to recognize intracellular tumor-specific proteins, which significantly limits the number of potential molecules to target. In contrast, TCRs recognize all cellular antigens that have been presented by MHC molecules, enabling T cells to recognize and attack cancer cells, including those expressing either intracellular or membrane-anchored tumor-specific proteins. However, despite the broader antigen recognition capabilities of TCR-Ts, the MHC-dependent mechanism requires careful tissue matching between the transgenic TCR and the patient, thus limiting the addressable patient population to only those patients with the appropriate MHC alleles. Finally, the targeted antigen for either CAR-T or TCR-T therapies must be shared broadly between patients. As a result, these therapies are not able to recognize unique, patient-specific antigens that may otherwise be attractive targets.

Overview of TIL Therapies

The application of TILs to treat solid tumors began in 1988, when these cells were first used as an experimental therapy at the U.S. National Cancer Institute. At that time, Steven A. Rosenberg, M.D., Ph.D. and his colleagues published results demonstrating melanoma regression in patients who had been treated with TILs grown *ex vivo*. Over the past 30 years, interest in TIL therapy for melanoma and other solid tumors has expanded significantly beyond academia, with dozens of academic and industry-sponsored clinical trials ongoing currently, ranging from Phase 1 exploratory trials of TILs in combination with a checkpoint inhibitor to Phase 3 randomized trials comparing TILs with established therapies.

A meta-analysis of clinical trials evaluating TIL therapies was published in the journal *Annals of Oncology* in 2019 and reported an ORR of 41% in 410 heavily pretreated patients with metastatic melanoma. Twelve percent of patients achieved CR with long-term durability, with only one of 28 patients experiencing disease recurrence.

We believe the following key factors are critical to the development of a patient-specific TIL-based therapy for the treatment of solid tumors:

Polyclonal recognition of tumor-specific antigens. TILs are activated to recognize and kill tumor cells based on their ability to bind to tumor-specific antigens. Unlike CAR-T cells and other engineered cell therapies that recognize only a single target antigen that is required to be both expressed on the surface of all tumor cells and shared across different patients, TILs are polyclonal and have the ability to recognize the broad set of antigens that are unique to each individual patient. This comprehensive, patient-specific polyclonality provides TIL therapies with the requisite diversity to respond to the marked clonal heterogeneity of the patient's tumors, addressing a major limitation of cell therapies such as CAR-Ts and TCR-Ts.

Optimized processing and manufacturing methods. TIL therapies rely on patient-derived material obtained from each patient's resected tumor. The processing methods for the freshly removed tumor tissue immediately following resection impact the characteristics of the final TIL product, including its potential efficacy. Streamlined and timely tumor procurement, processing and transportation is required to ensure manufacturing and clinical success.

The composition of the TIL population. TILs are immune cells naturally present in some tumors and composed of two types of T cells: CD8+ and CD4+ T cells. CD8+ T cells are cytotoxic T cells that are able to directly kill tumor cells. CD4+ T cells are T helper cells that secrete cytokines and engage in other activities to stimulate and recruit other immune cells, including other T cells, macrophages and dendritic cells, to tumor sites. Correlative studies have shown that high levels of T cells in tumors and surrounding tissues are associated with improved prognosis in a number of solid tumors, and the presence of both types of T cells is necessary for effective tumor control.

Our Approach

Our goal is to become the leader in the design, manufacture and delivery of TIL therapies to patients with cancer. We believe that the key elements that differentiate us include our highly experienced team, our optimized and scalable manufacturing process and our company-operated in-house manufacturing facilities.

Our Highly Experienced Team

We have assembled a team with extensive experience in the manufacture, clinical development and regulatory approval of cell therapies. Our process and engineering teams bring rigor to managing changes to our manufacturing processes based on their recognized track record in cell therapy research, development and commercialization. Our clinical operations team has developed CAR-T and TCR-T therapies in clinical trials across a wide variety of diseases, lines of therapy and patient populations across multiple geographies under the supervision of the FDA, the European Medicines Agency, or the EMA, and other leading regulatory agencies. We have operational know-how regarding tissue collection, chain of identity and custody, logistics and administration of autologous cell therapy products. Our team has a track record of successfully completing regulatory audits across multiple clinical trial sites, external vendors and internal processes. Notably, many members of our team were instrumental in the manufacture, clinical development and regulatory approvals of Yescarta and Tecartus.

Our Optimized and Scalable Manufacturing Process

We have designed our TIL manufacturing process to maximize manufacturing success rate and potential for clinical efficacy beyond current industry practices. To ensure product quality and consistency, we have chosen to maintain full control of the entire manufacturing process, from the procurement of tumor samples through the shipping of the final product, without any outsourcing of core manufacturing process or quality control testing steps. Our process includes the optimized cryopreservation of both the fully digested tumor at the beginning of the manufacturing process to preserve cell viability and potency and the final product at the end of the manufacturing process to provide increased shelf life. Importantly, our cryopreservation process also provides significant scheduling flexibility for physicians and patients, which may improve our ability to provide treatment to patients in a timely manner.

With our team’s extensive experience in the commercialization of cell therapies, we understand the feasibility and the value of continuous improvements in manufacturing. We have designed a robust quality system focused on compliance that includes routine testing for release, documentation of our processes and the assessment of the impact of any changes on final product performance. The quality of this data is essential as regulators rely on it to understand the relationship between products that may have been generated by modified or updated manufacturing procedures. In addition to our continuous refinements, we are also focused on longer-term manufacturing innovation initiatives that will drive generational changes to our manufacturing methods. For example, we are developing an automated, standardized platform to minimize manual processing and provide in-line process measurements that can be used to shorten manufacturing times, increase manufacturing success and reduce costs.

Another key component of the manufacturing process for cell therapies is the release criteria used to characterize the final product. We have developed and are validating a robust potency assay aimed at understanding the mechanism of action of our TIL therapies. Based on initial discussions with regulatory agencies regarding our potency assay and other release methods to support our IND approval, we believe that our assay methodology and final product release criteria will continue to satisfy guidelines and meet the expectations of the FDA and other regulatory authorities in support of BLA submission. Additionally, we have developed robust assays for purity, safety and dose designed to assure quality of our product. In addition to our release assays, we have generated a comprehensive package of characterization data as indicated by our IND approval.

Our Company-Operated In-house Manufacturing Facilities

We have expanded our manufacturing capabilities at our facilities in Manchester, United Kingdom, which has been operational since 2011, and are investing in expanding our manufacturing capabilities in the United States in

Tarzana, California, which became operational in the first half of 2022. Both facilities are fully controlled and operated by us, which will allow us to more efficiently introduce new product candidates and implement next-generation manufacturing technologies. In addition, by having facilities on two continents, we believe we have the ability to provide therapies, if approved, to patients across a broad geography as well as to continuously improve our operations.

Our clinical facility in Tarzana, which is expected to begin producing patient doses in the first half of 2022, has flexible modular technology using prefabricated modular cleanroom pods, enabling future process scalability and minimizing delays associated with the need for onsite construction. These modular cleanroom pods also provide the required segregation to allow for simultaneous manufacturing of distinct autologous products, such as ITIL-168 and ITIL-306, within the same manufacturing facility. Our clinical capacity is currently estimated up to approximately 150 patient doses per year with regulatory approval of our expanded facility in Manchester, U.K. Our Tarzana manufacturing facility will initially have a clinical capacity of up to 350 patient doses per year. We believe the aggregate capacity from these facilities will be sufficient for all of our planned clinical development activities. We are further expanding our capacity in Tarzana, California by establishing a commercial facility which we believe will be sufficient to meet the initial commercial demand of ITIL-168, if approved. With planned expansion of our commercial facility, we believe we could be able to support commercial demand of over 3,000 lots per year.

Our TIL Manufacturing Process

Our manufacturing process comprises three distinct and serial stages: (i) tumor processing, which includes tissue harvesting and cryopreservation, (ii) TIL generation, which includes the outgrowth and rapid expansion phases, and (iii) final product processing, which includes formulation and cryopreservation. We believe our novel approach to these three stages provides us with key advantages compared to historical approaches, as summarized below.

	Historical Approach	Our Novel Approach	Our Potential Advantages
Tumor Processing	• Transport of fresh tumor for continuous manufacturing • Fresh tumor fragments as starting material	• Cryopreservation and shipment of digested tumor • Fully digested tumor suspension as starting material	• More TILs are liberated from the digested tumor tissue, increasing clonal diversity in the final product • Enhanced cell viability and potency • Flexible patient scheduling and efficient manufacturing capacity utilization
TIL Generation	• Seeding of tumor fragments in open multi-well plates • TIL culture in plates with manual perfusion • Expansion of T cells in a static flask with manual controls • Manual media feed based on cell counts	• Seeding of tumor digest in closed gas-permeable culture bags • Expansion of T cells in a suspended bioreactor with process controls • Constant automated perfusion	• Closed processing and automated controls increase manufacturing robustness • More opportunities for optimization on bioreactor platforms vs. traditional flasks
Final Product Processing	• Manual formulation • Shipment of fresh final product	• Automated formulation • Shipment of cryopreserved final product	• Increased shelf life • Scheduling flexibility for physicians and patients

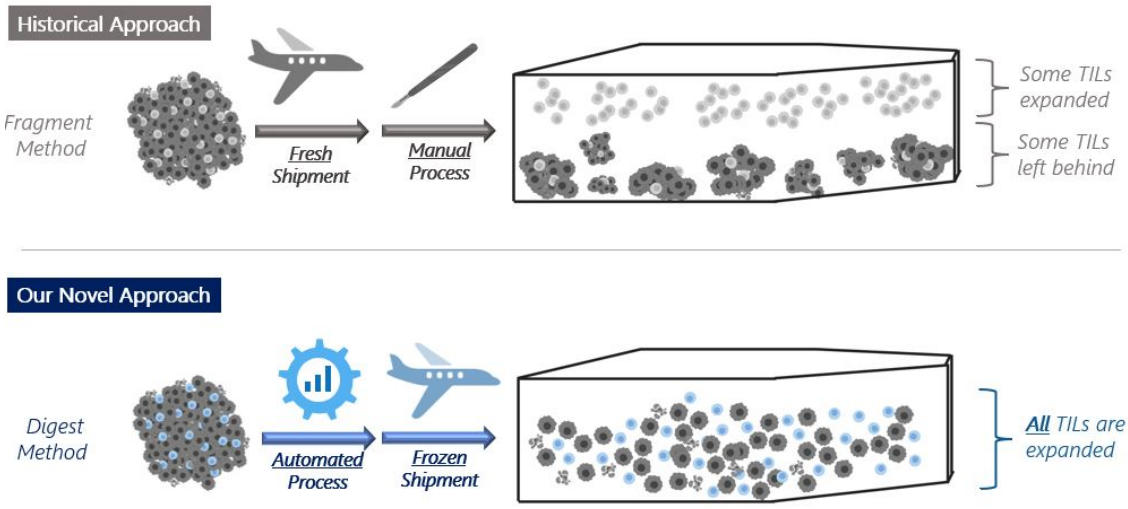
Tumor Processing

The starting material for our TIL product candidates is personalized with TILs isolated from a surgically excised sample of the patient's tumor. These tumor samples contain tumor cells, stromal cells and TILs. When TIL therapy was first developed in an academic research setting, the operating room in which the patient underwent the tumor resection procedure was in close physical proximity to the laboratory in which the TIL therapy was made.

Therefore, both the time required and the complexity of the transportation from operating room to manufacturing site were minimized. As TIL product candidates advance from single-institution clinical trials into registration-enabling global trials with multiple clinical sites and centralized manufacturing, controls for the stability of the removed tumor tissue must be instituted. We have developed a proprietary process in which the resected tissue is immediately processed and cryopreserved at one of our regional hubs located close to the clinical site, ensuring that our starting material is stable and preserved for shipment to one of our in-house manufacturing facilities for further processing.

The first step in our process involves fully dissociating the tumor tissue into a cell suspension through a combination of enzymatic digestion and gentle, automated agitation of the tissue. This initial step in our proprietary process has been designed to harvest all of the TILs embedded within the tumor without impacting cell viability. Our process is distinguished from typical manufacturing processes that start with manually minced fragments of tumor tissue. Our technique ensures that the greatest possible diversity of unique TCRs are preserved from the time of resection through the entire manufacturing process, as shown below:

Our Tumor Processing Method Releases and Preserves
All of the TILs from Tumor Samples



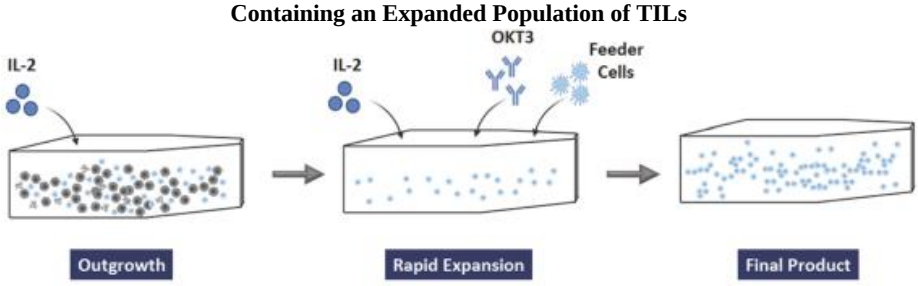
The rapid and reproducible stabilization of starting tumor material is crucial in enabling a scalable commercial process for treatment of patients across a broad geography. Logistical challenges, including coordination of patient scheduling with hospital availability, transportation of fresh tumor material and availability of manufacturing slots, have represented a significant barrier to the successful commercialization of autologous cell therapies. The process and infrastructure that we have developed to industrialize tumor procurement both preserves the starting tumor material and provides flexibility by allowing us to schedule tumor resection and TIL manufacturing independently from each other. Furthermore, once the starting material is cryopreserved, it can be stored for an extended period under controlled conditions before manufacturing begins, which reduces the risk of manufacturing failures due to tissue degradation and provides treatment flexibility for physicians and patients. Our novel approach will allow for the harvest of starting tumor material during routine biopsies or debulking surgeries for use in future TIL therapies.

In order to minimize the time from initial tumor resection to the processing, freezing and shipping of the tumor tissue, as part of our clinical trial, we plan to deploy a team of trained TIL recovery specialists to staff regional processing hubs strategically located near major treatment centers. The ability to have our specially trained staff take control of the tumor tissue as early in the process as possible and to process it using our proprietary methods helps ensure that the TILs in the starting material are of the highest possible quality and meet our manufacturing standards.

TIL Generation

The TIL generation step in our process includes the outgrowth and rapid expansion phases, as shown below, to ensure that our final TIL product contains an expanded population of TILs to maximize potential clinical efficacy.

The Outgrowth and Rapid Expansion of Our TILs Result in a Final Product Containing an Expanded Population of TILs



Outgrowth Phase. Once the cryopreserved tumor sample has reached one of our in-house manufacturing facilities, we thaw the suspension and culture the TILs and tumor cells together to promote the identification of tumor neoantigens by the TILs. This TIL outgrowth phase is designed to offer maximum exposure of the diverse and complete population of TILs to the clonally heterogenous tumor cells.

The complete tumor digestion that we utilize during the tumor processing step liberates all TILs from the tumor. During the outgrowth phase, all TILs are exposed to uniform concentrations of Interleukin-2, or IL-2, a potent T cell growth factor, in the cell suspension and freely associate with tumor cells. Our digestion process allows all of the harvested TILs to be collected and transitioned into the rapid expansion phase, or REP, of manufacturing and included in the final product. In contrast, the fragmentation method, in which a tumor specimen is manually minced into small fragments that are then cultured whole during outgrowth, relies on the migration of TILs out of the fragments by following an IL-2 gradient. Only those cells that successfully leave the tumor fragment and enter the bulk culture are collected and used to seed the REP of manufacturing; those that remain within the tumor fragment are discarded at the end of the outgrowth phase and thus are prevented from inclusion in the REP and final product. By the end of the TIL outgrowth phase in our process, the culture is predominantly composed of viable tumor-educated T cells, including CD8+ cytotoxic T cells and CD4+ helper T cells, and ready for further processing.

Rapid Expansion Phase. In the REP of manufacturing, we optimize the culture conditions to be conducive to the expansion of T cells that make up the final cell dose of the TIL therapy. We stimulate the cells with IL-2, OKT3, an anti-CD3 antibody that activates all TCRs, as well as feeder cells, which are peripheral blood mononuclear cells that support optimal growth conditions. Once sufficient expansion of the cell product has been reached to achieve what we define to be a therapeutic dose, the culture is harvested and prepared for final formulation and cryopreservation.

We believe our optimized and scalable manufacturing process provides several key advantages, including:

- The ability to capture and preserve maximum health and diversity of each patient's TILs by completely digesting and immediately cryopreserving the tumor sample near the clinical site to ensure stability during transportation to one of our in-house manufacturing facilities;
- A limited number of manual processing steps and a functionally closed manufacturing process to increase process reliability and scalability; and
- Flexibility to coordinate fresh tissue harvest with manufacturing availability through cryopreservation of both the starting material as well as the final product.

- The ability to capture and preserve maximum health and diversity of each patient's TILs by completely digesting and immediately cryopreserving the tumor sample near the clinical site to ensure stability during transportation to one of our in-house manufacturing facilities;
- A limited number of manual processing steps and a functionally closed manufacturing process to increase process reliability and scalability; and
- Flexibility to coordinate fresh tissue harvest with manufacturing availability through cryopreservation of both the starting material as well as the final product.

These attributes give us confidence that we will be able to deliver TIL-based therapies at a level of robustness, quality, consistency and scale not previously achieved by other TIL-based approaches.

Our Product Candidates

ITIL-168

Our lead TIL product candidate, ITIL-168, is an autologous TIL therapy that we are initially developing for the treatment of advanced melanoma. We have generated preliminary safety and efficacy data in advanced melanoma in the context of a compassionate use program using a TIL product that was produced with a prior version of the ITIL-168 manufacturing process. Twenty-one patients with stage IV metastatic cutaneous melanoma were treated between 2011 and 2019. Treatment led to an ORR of 67%, including four patients (19%) who achieved CR and ten patients (48%) who achieved PR. The DCR, which included patients with CR, PR or SD, was 86%. Based on these clinical results and our discussions with the FDA, we submitted an IND for ITIL-168 and, were authorized to initiate a Phase 2 trial in late 2021 with expected topline safety and efficacy data in 2023, which we believe could support a BLA submission. In addition to melanoma, we intend to initiate a Phase 1 trial of ITIL-168 in tumor types where evidence of immune cell recognition and elimination of cancer cells has been observed, such as CSCC, NSCLC, HNSCC and cervical cancer, in 2022.

Melanoma Overview

Melanoma is the most lethal form of skin cancer, accounting for the majority of skin cancer deaths. It arises from a malignant proliferation of melanocytes in the skin. The National Cancer Institute estimated that there would be more than 100,000 diagnoses of melanoma and 6,850 deaths from melanoma in the United States in 2020. Localized cutaneous melanoma is the fifth most common malignancy in the United States, and the incidence is rising. Most patients diagnosed with localized cutaneous melanoma have an excellent prognosis; however, in patients with distant metastatic spread of their disease, the 5-year survival rate is only 27%.

The primary risk factor for development of melanoma is exposure to ultraviolet, or UV, light, including sunlight and tanning beds. UV light and other environmental toxins can cause DNA damage, which, if not repaired, leads to an increased number of genetic mutations. In part due to this type of DNA damage, melanoma typically contains a high number of mutations. Furthermore, approximately half of melanomas have oncogenic driver mutations, such as alterations in the gene for proto-oncogene B-Raf, or BRAF. Both oncogenic driver and other mutations are an important differentiating feature between melanoma cells and healthy cells and form the pathophysiologic basis for recently developed therapeutic options.

Approximately one-half of cutaneous melanomas have an activating mutation in the BRAF gene. BRAF activates the mitogen-activated protein kinase, or MAPK, pathway, which accelerates the transformation of the cell into a cancer cell. BRAF inhibitors have demonstrated various positive clinical outcomes in melanoma, including tumor regression and survival improvement. Because many patients with BRAF mutations also have mutations in other oncogenes, the combination of a BRAF inhibitor with an inhibitor of mitogen-activated extracellular signal-regulated kinase, or MEK, an enzyme in the MAPK pathway, has been shown to further improve response rates and survival as compared with BRAF inhibition alone. Multiple BRAF inhibitors, such as vemurafenib (Zelboraf), dabrafenib (Tafinlar) and encorafenib (Braftovi), and MEK inhibitors, such as trametinib (Mekinist), cobimetinib (Cotellic) and binimetinib (Mektovi), have been approved for the treatment of metastatic melanoma.

More recently, multiple novel immunotherapies known as checkpoint inhibitors have been approved to treat advanced melanoma. These inhibitors block pathways such as PD-1/PD-L1 and CTLA4, which serve as negative regulators of T cell function. These groundbreaking therapies have changed the treatment landscape for metastatic melanoma and have dramatically improved both response rates and survival for patients.

Patients who are ineligible for surgery are typically treated with these systemic therapies. However, despite the significant response rates achieved with BRAF/MEK inhibitors and immunotherapies, a large proportion of patients either do not respond at all or develop resistance following an initial response and require additional therapy. Patients with melanoma that is refractory to or has relapsed following these treatments face a dearth of therapeutic options. There is no standard approach to the management of these patients and the limited number of agents used in this setting have shown poor response rates, high toxicity and limited survival benefit, as shown below.

Summary of Published Trials of Treatments for Patients with Advanced Melanoma

Lead Author (Year of Publication)	N	Treatment	ORR	Toxicity	Overall Survival
Zimmer (2017)	37	Ipilimumab + nivolumab	21%	33% discontinuation	55% (1 year)
Bowyer (2016)	40	Ipilimumab	10%	35% grade 3+ immune-related adverse events (AEs)	Not reported (median progression free survival of 5 months)
Kirchberger (2016)	9	Low dose ipilimumab + pembrolizumab	0%	Minimal	8 months (median)
Aya (2016)	9	Ipilimumab	22%	56% grade 3+ immune-related AEs	Not reported (median progression free survival of 3.1 months)
Weichenthal (2019)	200	Various	4-22%	10-36% grade 3+ AEs or discontinuation	9.2 – 15.6 months
Buchbinder (2019)	40	High dose IL-2	23%	20% discontinuation after one cycle	29.4 months

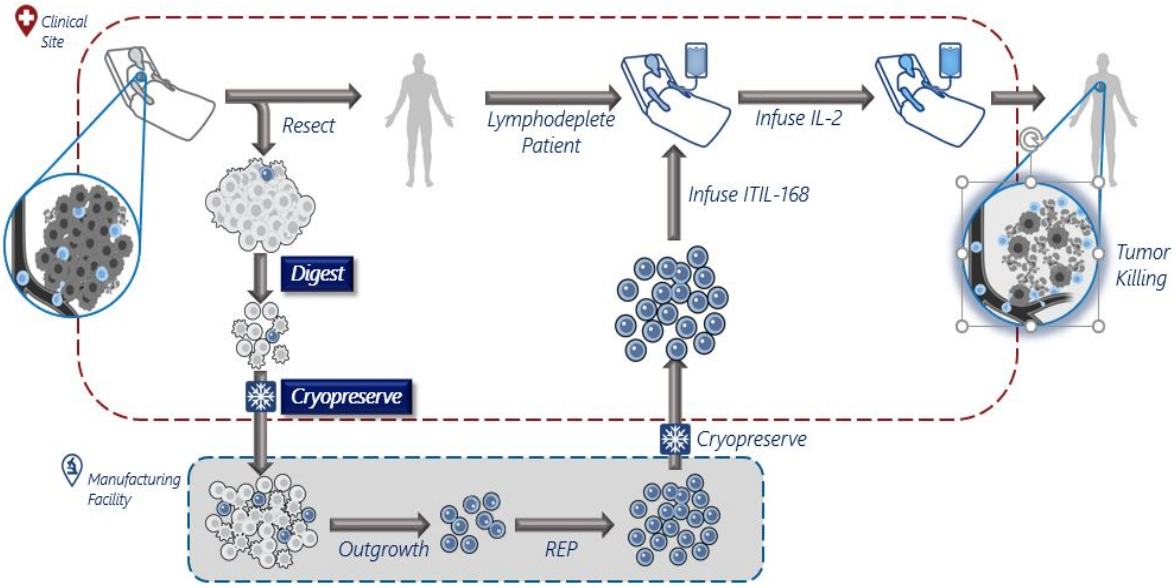
According to the scientific literature, TIL therapy is considered one of the most effective treatments for patients with advanced melanoma, including following the failure of checkpoint inhibitors and BRAF/MEK inhibitors. However, because of the complexity in scaling autologous cell therapies, including TIL therapy, access to this potentially life-saving treatment has been limited to patients who are enrolled in clinical trials or treated under compassionate use. Furthermore, the majority of these TIL therapy clinical trials have been conducted in single academic centers with little standardization in the manufacturing methods used to isolate, activate and expand the TILs that comprise the final product. We believe our optimized process will enable the standardization and scaling of the manufacture of our lead TIL product candidate, ITIL-168, to provide significant clinical benefit for patients with advanced melanoma.

Our Solution: ITIL-168

We initiated a global, multi-center Phase 2 clinical trial of ITIL-168 in PD-1-inhibitor relapsed or refractory advanced melanoma in late 2021 and intend to initiate a multi-center Phase 1 clinical trial of ITIL-168 in several solid tumor types in 2022. Our process for ITIL-168 begins with the procurement of the resected tumor by one of our trained specialists. At one of our regional processing hubs located near the clinical site, the resected tumor is placed into a sterile bag containing media and tissue digestion enzymes. The bag is then heat-sealed and its contents are digested through a process of gentle agitation and enzymatic activity to generate a homogeneous cell suspension containing tumor cells and TILs. This proprietary method allows for the complete digestion of the tumor tissue and

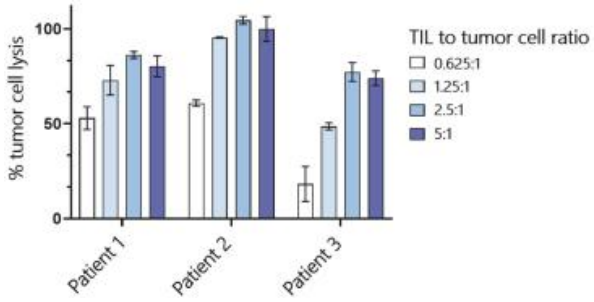
releases all of the TILs from the tumor microenvironment. The cell suspension is then cryopreserved and shipped to one of our in-house manufacturing facilities, where it is thawed. The process of activating and expanding the TILs is then initiated. Upon completion of manufacturing, the final product candidate is formulated and cryopreserved for shipment back to the clinical site. Following treatment with lymphodepleting chemotherapy and ITIL-168, the patient is treated with IL-2 to support the further proliferation of ITIL-168 *in vivo*. The manufacturing period takes approximately 24-25 days based on our current processes. Our manufacturing and treatment process for ITIL-168 is summarized in the graphic below:

The ITIL-168 Manufacturing and Treatment Process



A preclinical study of TILs made from three separate patients using a process similar to ITIL-168 consistently killed tumor cells. In addition, this study showed dose-dependent anti-tumor activity *in vitro* with evidence of tumor killing even at low TIL to tumor cell ratios, as shown below:

A Preclinical Study Demonstrated Dose-Dependent Anti-Tumor Activity *In Vitro*



Clinical Data from Compassionate Use Program

We have generated preliminary safety and efficacy data from a compassionate use program in the United Kingdom in advanced melanoma using a TIL product that was manufactured using a prior version of the ITIL-168 manufacturing process. The compassionate use program was authorized under a Manufacturing Specials license from the Medicines and Healthcare products Regulatory Agency. Individual patients were referred by their local oncologists to Professor Robert Hawkins, MBBS FRCP, Ph.D., our Chief Strategy Advisor and a well-known medical oncologist and cell therapy investigator at the Christie Hospital in Manchester, United Kingdom, for evaluation and treatment.

Between 2011 and 2019, a total of 21 patients with stage IV metastatic cutaneous melanoma received approximately the same treatment regimen we intend to evaluate in our clinical trials of ITIL-168: lymphodepleting chemotherapy, TIL infusion and post-TIL IL-2 treatment. The majority of these patients had metastases to the lung and other non-CNS sites, referred to as stage M1c disease, or brain metastases, referred to as stage M1d disease, including 14 patients who had metastatic lesions in more than three sites and seven patients who had brain metastases. These patients were referred to Dr. Hawkins after being treated with and failing an average of three prior systemic therapies. Over 90% of the patients had failed the CTLA4 inhibitor ipilimumab, and 12 patients had experienced disease progression on or following treatment with a PD-1 inhibitor as well as ipilimumab. More than half of the patients had a BRAF mutation and had progressed on a BRAF inhibitor.

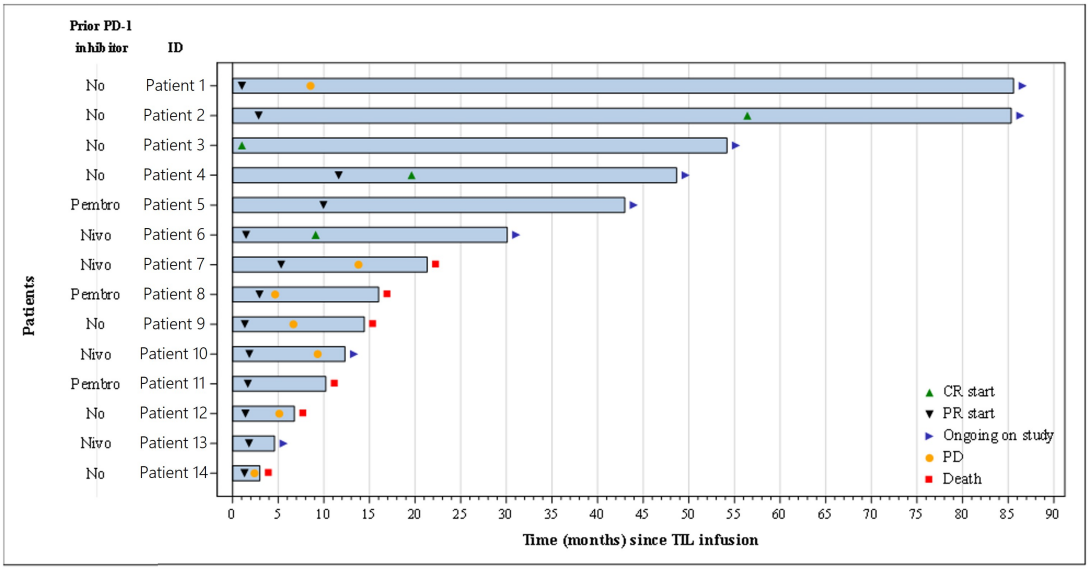
As shown in the table below, treatment with TIL therapy led to an ORR of 67% in these 21 patients, including four patients (19%) who achieved CR and 10 patients (48%) who achieved PR. The DCR, which included 4 patients with SD in addition to those with CRs and PRs, was 86%. Of these 21 patients, 15 were followed up with CT and/or MRI at regular intervals in a manner consistent with standard RECIST 1.1 methodology; in this subgroup of patients, the ORR was 53% and the CR rate was 13%. The other six patients were followed with non-RECIST imaging modalities like PET/CT as well as clinical monitoring. Two of these six patients had developed melanoma that was unequivocally refractory to the BRAF inhibitor dabrafenib in combination with MEK inhibitor therapy immediately prior to TIL treatment but were continued on dabrafenib, with brief interruptions for tumor harvest and TIL infusion, to prevent the rapid disease progression that often accompanies abrupt dabrafenib discontinuation. Both patients developed durable responses following TIL treatment. One patient, who had also failed prior ipilimumab and PD-1 blockade, achieved a PR that lasted approximately 14 months from TIL infusion during which time dabrafenib was continued. The second patient was treated with dabrafenib for approximately three months following TIL infusion, at which point the dabrafenib was stopped. This patient achieved a PR at approximately 12 months after TIL infusion that converted to a durable CR that was ongoing for over four years after TIL infusion at the time of data cutoff.

Summary of Responses in All Patients Treated in Compassionate Use Program (n=21)

	n (%)
Overall remission rate	14 (67%)
Partial remission rate	10 (48%)
Complete remission rate	4 (19%)
Disease control rate	18 (86%)

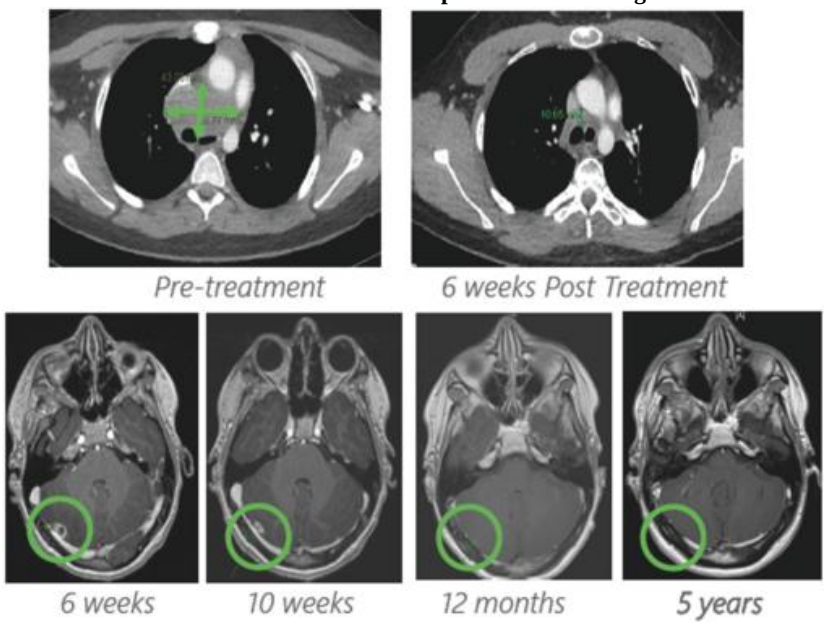
Eight of the 14 responders were still alive as of the data cutoff date of December 31, 2019, with all four patients with CRs remaining without disease progression, as shown below.

Treatment with TIL Therapy Led to Long-term Survival of Patients with Metastatic Melanoma in Compassionate Use Program



One of the responding patients in the compassionate use program was a 16-year-old male with widely metastatic and bulky (sum of lesion diameters = 103mm), BRAF-mutated melanoma that was refractory to three prior lines of therapy, including ipilimumab, a CTLA4 inhibitor, and dabrafenib, a BRAF inhibitor. Following treatment with TIL therapy, this patient experienced a rapid reduction in his disease burden, as shown in the images below. Over the following year, repeated scans confirmed continued reduction in his systemic and brain metastases, and he subsequently achieved CR and has remained without disease progression for over seven years.

Ongoing Complete Remission at 7+ Years in a 16-Year-Old Patient with Metastatic Melanoma in Compassionate Use Program



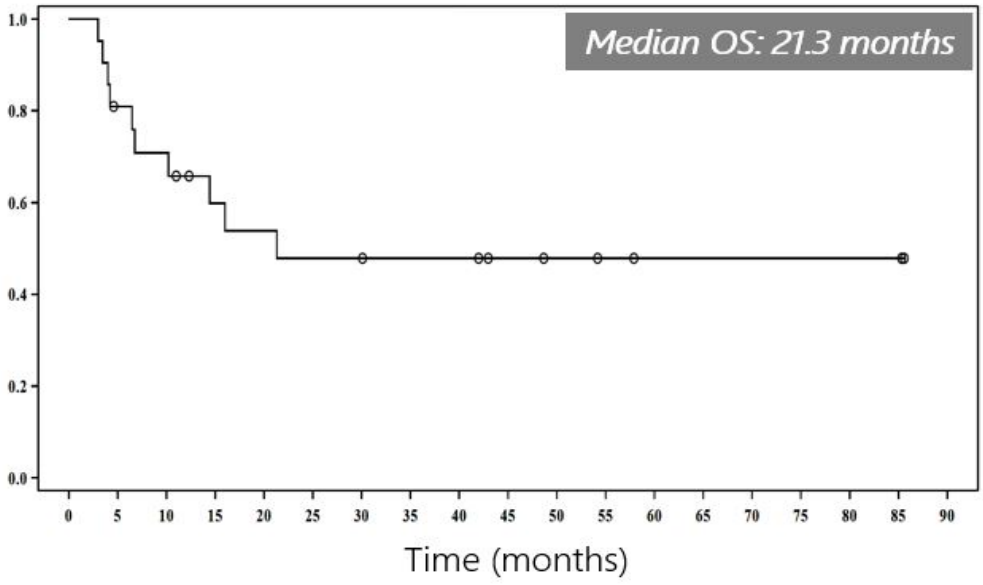
Among the 12 patients who had previously failed at least one PD-1 inhibitor as well as ipilimumab, seven patients (58%) achieved a remission, including one (8%) who achieved CR. The DCR, which included two patients with SD, was 75%, as shown in the table below.

Summary of Responses in Patients with PD-1 and CTLA4 Inhibitor Relapsed or Refractory Melanoma in Compassionate Use Program (n=12)

	n (%)
Overall remission rate	7 (58%)
Partial remission rate	6 (50%)
Complete remission rate	1 (8%)
Disease control rate	9 (75%)

The median time to response in all 21 patients was under 2 months and the median overall survival was 21.3 months, as shown in the Kaplan-Meier survival graph below. The results from the compassionate use program do not provide a guarantee that ITIL-168 will be deemed to be safe or effective for the treatment of melanoma or additional indications, and extensive clinical testing and regulatory approval will be required before ITIL-168 can be commercially marketed for the treatment of melanoma.

Survival of Patients with Advanced Melanoma Treated with TIL Therapy in Compassionate Use Program



Safety

Overall, the safety findings associated with the TIL regimen of lymphodepletion, TIL transfusion and post-TIL IL-2 treatment was consistent with the published literature of TIL therapy in patients with melanoma. Side effects were largely transient, self-limited and generally attributable to the lymphodepleting chemotherapy regimen and post-TIL IL-2 treatment. The most common adverse events, or AEs, after the TIL infusion were transient low blood counts and physiological manifestations of IL-2, including fever, tachycardia and edema. There were no deaths deemed related to the treatment regimen. As of the data cutoff date, 10 of 21 patients had died due to complications arising from disease progression.

AEs experienced by patients in this compassionate use program were not systematically graded by the treating physicians nor was AE attribution or seriousness consistently collected. Rather, AEs were summarized by signs and symptoms and according to the time of onset relative to the treatment sequence. The most frequently reported AEs during the lymphodepleting chemotherapy period were neutropenia (nine patients, 43%) and nausea (four patients, 19%). All other AEs were reported in one patient (5%) each. The most frequently reported AEs after TIL infusion were thrombocytopenia (13 patients, 62%), pyrexia (12 patients, 57%) and rigors (nine patients, 43%). Neutropenia and tachycardia were experienced by six patients (29%) each; pulmonary edema and vascular leak were each observed in five patients (24%). Rash was observed in four patients (19%) and atrial fibrillation, cardiovascular instability, chest infection and oedema were each observed in three patients (14%). All other AEs occurred in two or fewer patients (<10%).

Clinical Development Plans

Based on the results from the compassionate use program, we submitted an IND and were authorized to proceed with a Phase 2 trial of ITIL-168 in patients with PD-1-inhibitor relapsed or refractory advanced melanoma in the late 2021. We anticipate obtaining topline safety and efficacy data in 2023, and we believe this Phase 2 trial, if successful, has the potential to support the submission of a BLA to the FDA and a Marketing Authorization Application to the EMA.

We designed our Phase 2 trial to enroll approximately 130 patients who have relapsed or refractory cutaneous melanoma. There are three patient cohorts in the study design: Cohort 1 (approximately 80 patients) includes patients who have failed treatment with a PD-1 inhibitor and, if applicable, a BRAF inhibitor; Cohort 2 (approximately 25 patients) includes patients who discontinued PD-1 inhibitor therapy due to intolerable toxicity; Cohort 3 (approximately 25 patients) includes patients who had an unsatisfactory response to prior PD-1 inhibitor but have not yet experienced disease progression. Patients will undergo surgery to remove a small amount of their tumor to initiate the manufacturing process. Once the patient-specific ITIL-168 is fully manufactured and sent back to the clinical site, patients will be treated with lymphodepleting chemotherapy. ITIL-168 infusion will be followed by treatment with IL-2 to support the further proliferation of ITIL-168 *in vivo*. The primary endpoint of this trial will be ORR, with secondary endpoints focusing on additional aspects of safety and efficacy.

Clinical Development for ITIL-168 in Additional Tumor Types

We intend to initiate clinical trials of ITIL-168 in other solid tumor types where evidence of immune cell recognition and elimination of cancer cells has been observed. We plan to evaluate ITIL-168 for the treatment of relapsed or refractory NSCLC, HNSCC and cervical cancer. Third-party TIL therapy has demonstrated clinical proof of concept in each of these tumor types, with an ORR of 31% reported in a clinical trial of a third-party TIL therapy for the treatment of HNSCC, an ORR of 25% reported in a clinical trial of a third-party TIL therapy for the treatment of NSCLC, and an ORR of 44% reported in a clinical trial of a third-party TIL therapy for the treatment of cervical cancer. We also plan to evaluate ITIL-168 for the treatment of relapsed or refractory, locally advanced or metastatic CSCC. All of these tumor types continue to have an unmet medical need. In 2019, the annual mortality of NSCLC, HNSCC and cervical cancers in the U.S. surpassed 120,000, 10,000, and 4,000, respectively. We expect to file another amendment to our IND for ITIL-168 and initiate a multi-indication Phase 1 trial in 2022. Following this trial, if successful, we anticipate opening Phase 2 trials within each of these four tumor types to evaluate the safety and efficacy of ITIL-168 in these indications.

CoStAR: A Co-stimulatory Platform to Genetically Engineer TILs

We are developing a novel class of genetically engineered TIL product candidates designed to express Co-Stimulatory Antigen Receptor, or CoStAR, molecules to augment the activation of TILs in the tumor microenvironment, potentially leading to an increase in anti-tumor activity. We believe that the ability of CoStAR to enhance the activation of TILs upon recognition of tumor neoantigens has the potential to bring TIL therapy to patients with cancer types that historically have been resistant to immunotherapy. In preclinical studies, we observed that CoStAR+ T cells demonstrated markedly increased activity as compared to normal T cells, including enhanced cytokine expression and proliferative capacity. We are leveraging the optimized and scalable manufacturing process that we have developed for ITIL-168 to develop manufacturing process steps specific to CoStAR-TIL therapies.

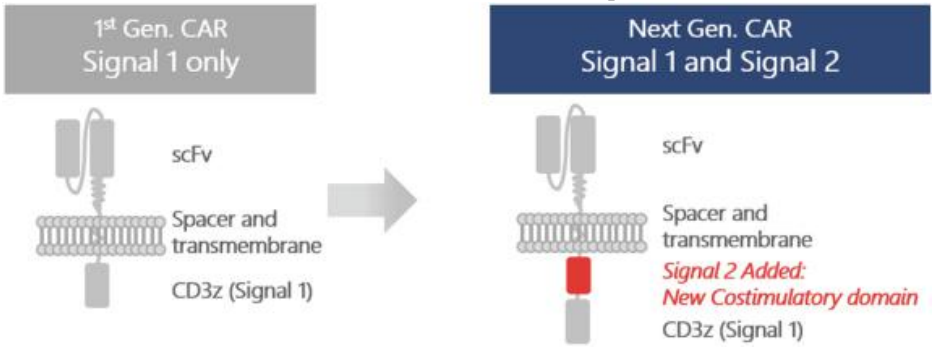
We plan to evaluate CoStAR-TIL therapies in several tumor types where TILs have not yet established proof of concept or responses to TIL therapy have been poor. We anticipate submitting an IND for our lead CoStAR-TIL product candidate, ITIL-306, in 2022.

Role of Co-stimulation in T Cell Activation

Activation of T cells typically requires more than the recognition of an antigenic peptide bound to the MHC on the surface of a target cell. Maximum T cell activation generally requires both this antigen-specific signal and a second, antigen-independent signal known as costimulation. Costimulation occurs when a costimulatory molecule

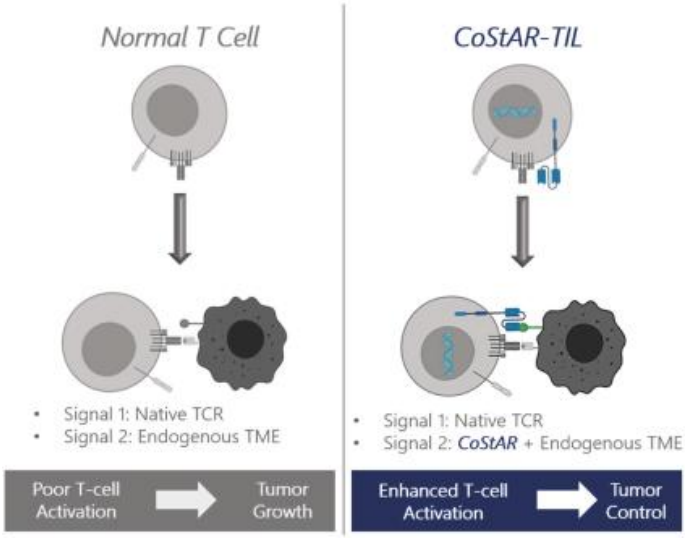
on the surface of the T cell binds to its ligand on the target cell at the same time that the TCR is engaging with the antigen presented by the MHC. The requirement for costimulation also applies to T cell therapies. For example, first generation CAR-T therapies did not contain any additional costimulatory molecules, as shown below, and therefore relied on endogenous co-stimulation for enhanced activity within the tumor microenvironment. As a result, the anti-tumor activity of these first-generation products was low. Subsequent generations of CAR-T therapies included one or more costimulatory domains, which have been shown to increase their anti-tumor activity. However, these therapies are still bound by the limitations of single-antigen targeting, including on-target, off-tumor toxicities.

Costimulatory Domains in First Generation vs.
Next-Generation CAR-T Therapies



Design and Intended Function of CoStAR

Our CoStAR platform encompasses a class of novel CARs designed to increase the anti-tumor activity of our TIL product candidates by providing potent co-stimulation via two intracellular costimulatory domains that are linked by a transmembrane sequence to an extracellular single chain variable fragment, or scFv. When CoStAR is expressed on the surface of TILs, the scFv is designed to bind to commonly expressed, shared tumor-associated antigens and thereby deliver a potent costimulatory signal to the T cell. This costimulatory signal is only relevant when the TIL's native TCR engages a tumor-specific neoantigen on the surface of the tumor cell, as shown below. In preclinical studies, we did not observe any measurable effects of CoStAR engagement of the shared tumor-associated antigen on the T cell without concomitant TCR recognition of a tumor neoantigen.



The main difference between CoStAR and second or later generation CARs is that CoStAR is designed to exclusively induce co-stimulation. This effect is achieved by the elimination of the CD3ζ signaling domain that is uniformly included in CAR-T products. Absence of the CD3ζ domain renders CoStAR ligation alone unable to lead to T cell activation or cytolytic activity. Similar to ITIL-168, the full activation of CoStAR+ T cells is first dependent on the recognition of tumor-specific antigens by the native TCR. The CoStAR modification only serves to augment the activation of the T cells once TCR binding has occurred. In preclinical studies, we did not observe any measurable effects of CoStAR engagement of the shared tumor-associated antigen on the T cell without concomitant TCR recognition of a tumor neoantigen.

We believe the separation of function between tumor recognition and activation in our CoStAR-TILs provides the following key advantages compared to CAR-T therapies:

Increased potency without a change in specificity. The introduction of a CAR to a T cell fundamentally changes its specificity to target cells that express the antigen bound by the scFv of the CAR. Because the target antigen is not unique to individual tumor cells, CAR-T cells kill any cells that express this antigen, including healthy cells. This lack of discrimination often results in on-target, off-tumor toxicity, as observed with anti-CD19 CAR-T therapies that eliminate normal B cells that express CD19, causing prolonged immunosuppression. In contrast, CoStAR does not change the specificity of TILs, as T cell activation is still entirely dependent on the recognition by the cell's native TCR of a unique tumor neoantigen presented by the target cell. CoStAR strictly provides the necessary costimulatory signal for full T cell activation. Through the selection of the specific scFv incorporated into the CoStAR architecture, costimulation is triggered in a tumor-specific manner, providing a microenvironment-specific signal leading to increased TIL activation.

Retention of polyclonal antigen recognition. Our CoStAR-TILs rely on the unique endogenous TCRs expressed by each T cell to recognize the heterogeneous set of tumor neoantigens that are presented by tumor cells. With CoStAR-TIL therapy, the T cells isolated directly from the patient's tumor have been naturally selected by the immune system and preserved by our manufacturing process to target patient-specific neoantigens. We believe the ability to target multiple antigens is critical to the success of cell therapies in solid tumors due to the intra-tumor heterogeneity of cancer cells in solid tumors and the limited success observed with single-antigen cell therapy approaches to date.

Enhanced cytokine secretion and profile. Our CoStAR-TIL product candidates are designed to secrete high levels of activating cytokines into their surrounding microenvironment upon the engagement of unique tumor neoantigens by the TILs' native TCRs in combination with the engagement of the target by CoStAR. Additionally, the production of immunosuppressive cytokines is reduced. We believe that these properties of our CoStAR-TILs will stimulate immune cell migration into tumors, which may, in turn, drive additional immune reaction to the tumor, resulting in the conversion of poorly immunogenic tumors with few endogenous immune cells into inflamed tumors with a broad array of activated immune cell subsets. Such inflamed tumors have been shown to be more amenable to treatment with immunotherapies and to have better prognosis.

Broad platform targeting shared tumor-associated antigens. A defining feature of our CoStAR platform is its expected safety profile. Unlike conventional ADC or CAR-T therapies, CoStAR's engagement with the cell expressing its target antigen alone does not trigger its elimination. This key attribute allows us to consider a wide array of antigens to target with our CoStAR-TIL product candidates with fewer concerns related to safety risk associated with normal tissue expression. In addition to the tumor-associated antigens commonly targeted by other therapeutic modalities, such as HER2, CoStAR may have the potential to target other antigens, including those with extensive normal tissue expression.

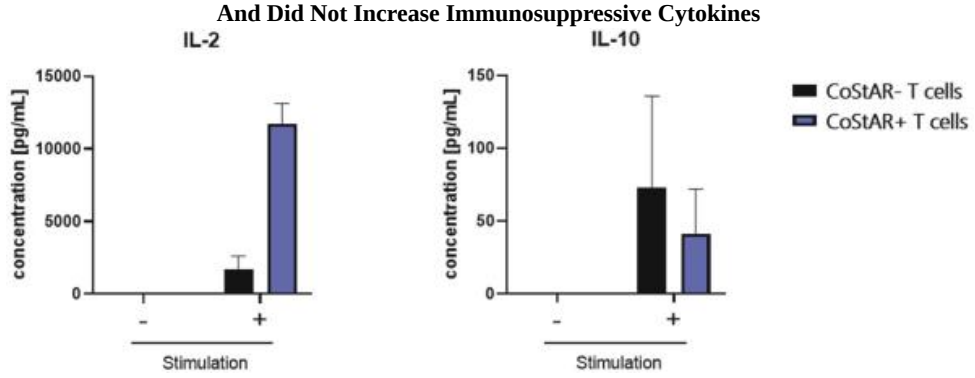
Our CoStAR Platform

During our development of the CoStAR platform, we empirically designed and tested a number of sequences containing various costimulatory domains, either as single domains or as pairs of domains, to identify the most potent architecture using a variety of target antigens. We found that the inclusion of a particular configuration of two

costimulatory domains led to markedly enhanced cytokine secretion, cell survival and proliferation *in vitro* as compared to the other tested variants.

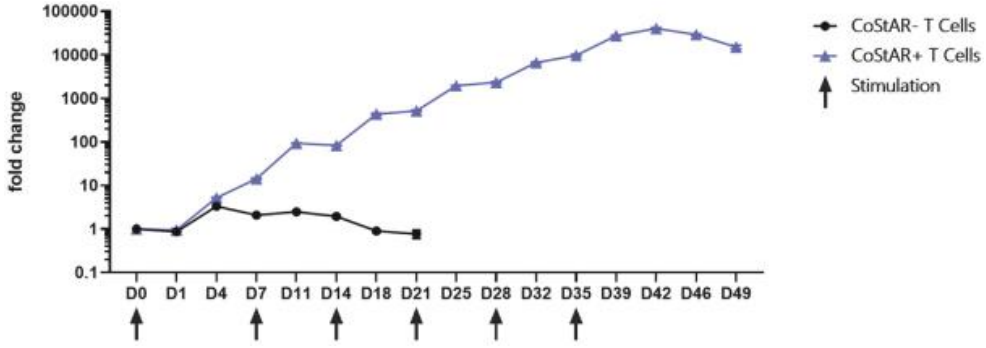
We observed increased expression of certain pro-inflammatory cytokines, such as IL-2, without increased expression of immunosuppressive cytokines, such as IL-10, that are known to be detrimental to T cells and other immune subsets, as shown below, which we believe is due to the design of the signaling domains in CoStAR. We believe that CoStAR's ability to increase pro-inflammatory cytokines with no significant rise in immunosuppressive ones creates a favorable immunological milieu that may promote a robust anti-tumor response.

CoStAR Increased Pro-inflammatory Cytokines
And Did Not Increase Immunosuppressive Cytokines



In multiple third-party CAR-T therapy clinical trials, post-infusion expansion of T cells has been shown to correlate with deep and durable clinical responses in patients. The *in vitro* expansion of T cells demonstrated in our preclinical studies, even in stringent culture conditions that lack supplemental IL-2, provides preclinical evidence of the improved proliferative capacity of CoStAR+ T cells. As shown below, CoStAR+ T cells responded to target cells that expressed OKT3, an anti-CD3 antibody that activates all TCRs, and the CoStAR target with increased survival and proliferation as compared to CoStAR- T cells.

CoStAR+ T Cells Showed Increased Survival and Proliferation of Cells in the Absence of IL-2



Our preclinical studies of CoStAR+ T cells have demonstrated the potential of CoStAR-TIL therapies to increase anti-tumor activity compared to conventional TIL therapies. Specifically, the CoStAR platform:

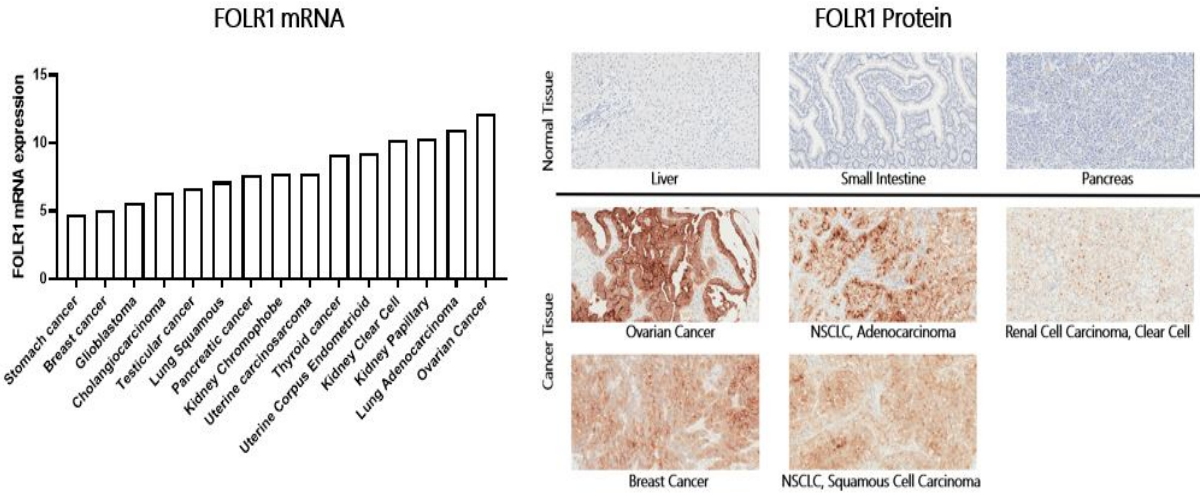
- Retained the anti-tumor TCR repertoire of the starting TIL population, thus reducing the potential for normal tissue toxicity;

- Demonstrated markedly increased survival and growth potential and reduced dependence on supplemental IL-2 in response to target cells expressing OKT3 and the CoStAR target; and
- Secreted high levels of immune-activating cytokines like IL-2 without increased expression of immunosuppressive cytokines, which we believe offers the potential for a potent bystander effect in the tumor microenvironment.

Our Lead CoStAR-TIL Product Candidate, ITIL-306

Our first CoStAR-TIL product candidate, ITIL-306, is an autologous TIL therapy genetically engineered to express a CoStAR molecule that recognizes FOLR1. FOLR1 is a tumor-associated antigen that is expressed on numerous solid tumors, including ovarian, uterine, NSCLC and renal cancers. As shown in the immunohistochemical, or IHC, stains below, FOLR1 is found to be expressed at high levels in numerous solid tumor indications and its expression in normal tissue is minimal. The FOLR1-CoStAR candidate stimulates T cells through a novel combination of intracellular domains from CD40 and CD28, which was shown to markedly outperform other combinations of costimulatory domains in various *in vitro* assays. ITIL-306 will be manufactured with a 21-day manufacturing process that has demonstrated robust transduction of TILs in our process development studies.

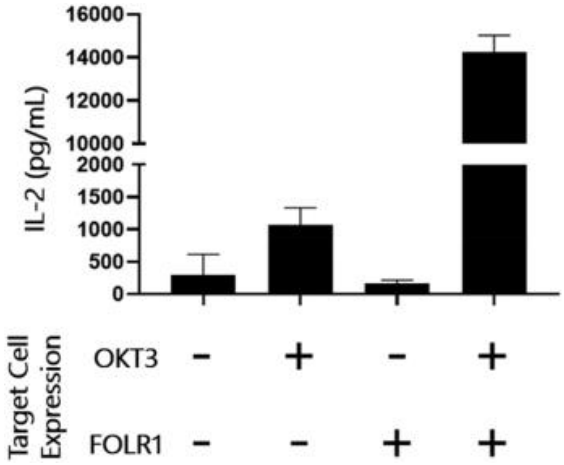
FOLR1 is Expressed by Numerous Solid Tumors,
as Assessed by mRNA and Protein



To validate that FOLR1-CoStAR TILs are robustly activated only in the presence of FOLR1 and native TCR stimulation, we assessed the ability of CoStAR+ T cells to secrete IL-2 in an *in vitro* study. Cytokine secretion is a classical measure of activation of T cells and represents a key mechanism by which CoStAR+ T cells enhance the tumor microenvironment and proliferation of TILs. These CoStAR+ T cells were cultured with target cells that were engineered to express OKT3, FOLR1, neither of these molecules, or both.

As shown below, the culture with OKT3-expressing target cells yielded a modest increase in IL-2 secretion over baseline. The addition of CoStAR costimulation, as shown by the FOLR1 expression in the target cells, led to an approximately 10-fold increase in IL-2 secretion. Importantly, ligation of CoStAR by FOLR1 alone in the absence of TCR engagement led to no measurable increase over baseline IL-2 secretion, supporting that the delivery of costimulation through the CoStAR molecule alone does not activate T cells. This finding supports our hypothesis that CoStAR will limit the on-target, off-tumor toxicity that is often found with classical CAR-T therapies, while enhancing T cell activation within the tumor.

CoStAR+ T Cells Enhanced Secretion of IL-2 in the Presence of Both FOLR1 and Activated TCRs



We intend to submit an IND for ITIL-306 in 2022. Further preclinical and manufacturing development of ITIL-306 will inform the final clinical development plan and first-in-human study design. We anticipate initiating a Phase 1 trial in 2022 to evaluate preliminary safety, feasibility and efficacy in multiple tumor types.

Additional CoStAR-TIL Programs

The modular nature of our CoStAR platform allows for multiple product candidates to be developed with minimal changes to the fundamental architecture of the molecule. We have generated a number of constructs containing antigen-binding domains directed against different tumor-associated antigens that are expressed by a wide variety of tumor types, including stomach, colorectal, pancreatic, breast and other cancers. We have identified construct families for our next CoStAR-TIL product candidate, and we intend to select our next CoStAR-TIL product candidate for IND-enabling studies in 2022.

Commercialization Plan

We are in the process of building our U.S. commercial and medical affairs infrastructure and intend to build our own global commercialization capabilities over time in certain geographies for our TIL product candidates, including ITIL-168 and ITIL-306. If any of our TIL product candidates are approved, we expect to commercialize those products with an experienced sales, marketing and distribution organization, including a national specialty oncology sales force. As additional product candidates advance through our pipeline, our commercial plans will evolve as we consider elements such as the market potential.

Competition

The biotechnology and pharmaceutical industries are characterized by the rapid evolution of technologies and understanding of disease etiology, intense competition and a strong emphasis on intellectual property. We believe that our approach, strategy, scientific and manufacturing capabilities, know-how and experience provide us with competitive advantages. However, we expect substantial competition from multiple sources, including major pharmaceutical, specialty pharmaceutical, and existing or emerging biotechnology companies, academic research institutions and governmental agencies and public and private research institutions worldwide. Many of our competitors, either alone or through collaborations, have significantly greater financial resources and expertise in research and development, manufacturing, preclinical testing, conducting clinical trials, obtaining regulatory approvals and marketing approved products than we do. Smaller or early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies. These entities also compete with us in recruiting and retaining qualified scientific, manufacturing and management

personnel and establishing clinical trial sites and patient enrollment in clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs. As a result, our competitors may discover, develop, license or commercialize products before or more successfully than we do.

We face competition from segments of the pharmaceutical, biotechnology and other related markets that pursue the development of TIL or other cell therapies for the treatment of solid tumors. Companies that are developing TIL therapies include Iovance Biotherapeutics Inc., Adaptimmune Therapeutics, Plc., Achilles Therapeutics, Ltd., Intima Bioscience, Inc., Nurix Therapeutics, Inc., KSQ Therapeutics, Inc., Obsidian Therapeutics, Inc., PACT Pharma, Inc., Lyell Immunopharma, and Neogene Therapeutics, B.V. In addition, we may face competition from companies focused on CAR-T and TCR-T cell therapies, such as Kite Pharma, Inc., a subsidiary of Gilead, Inc., Juno Therapeutics, Inc., a subsidiary of Bristol-Myers Squibb, Inc., TCR2 Therapeutics, Inc., Poseida Therapeutics, Inc. and Immatics N.V. There are also companies utilizing other cell-based approaches that may be competitive to our product candidates. For example, companies such as Celyad, S.A., Artiva Biotherapeutics, Inc., and Nkarta, Inc. are developing therapies that target and/or engineer natural killer, or NK, cells.

Furthermore, we also face competition more broadly across the oncology market for cost-effective and reimbursable cancer treatments. The most common methods of treating patients with cancer are surgery, radiation and drug therapy, including chemotherapy, hormone therapy, biologic therapy, such as monoclonal and bispecific antibodies, immunotherapy, cell-based therapy and targeted therapy, or a combination of any such methods. There are a variety of available drug therapies marketed for cancer. In many cases, these drugs are administered in combination to enhance efficacy. While our TIL product candidates, if any are approved, may compete with these existing drugs and other therapies, to the extent they are ultimately used in combination with or as an adjunct to these therapies, our TIL therapies may not be competitive with them. Some of these drugs are branded and subject to patent protection, and others are available on a generic basis. Insurers and other third-party payors may also encourage the use of generic products or specific branded products. As a result, obtaining market acceptance of, and gaining significant share of the market for, any of our TIL therapies that we successfully introduce to the market may pose challenges. In addition, many companies are developing new oncology therapeutics, and we cannot predict what the standard of care will be as our product candidates progress through clinical development.

We could see a reduction or elimination in our commercial opportunity if our competitors develop and commercialize drugs that are safer, more effective, have fewer or less severe side effects, are more convenient to administer, are less expensive or with a more favorable label than our TIL product candidates. Our competitors also may obtain FDA or other regulatory approval for their drugs more rapidly than we may obtain approval for ours, which could result in our competitors establishing a strong market position before we are able to enter the market. The key competitive factors affecting the success of all of our TIL product candidates, if approved, are likely to be their efficacy, safety, convenience, price and the availability of reimbursement from government and other third-party payors.

Intellectual Property

Our commercial success may depend in part on our ability to obtain and maintain patent and other proprietary protection for commercially important technology, inventions, improvements and know-how related to our business; defend and enforce our patents and other intellectual property; preserve the confidentiality of our trade secrets; and operate without infringing or otherwise violating the valid enforceable patents and proprietary rights of third parties. Our ability to stop third parties from making, using, selling, offering to sell or importing our products may depend on the extent to which we have rights under valid and enforceable patents or trade secrets that cover these activities. With respect to both licensed and company-owned intellectual property, we cannot be sure that patents will be granted with respect to any of our pending patent applications or with respect to any patent applications filed by us in the future, nor can we be sure that any of our existing patents or any patents that may be granted to us in the future will be commercially useful in protecting our commercial products and methods of manufacturing the same. We may rely, in some circumstances, on trade secrets to protect our technology. However, trade secrets can be difficult to protect. See “Risk Factors – Risks Related to Our Intellectual Property.”

We actively seek to protect our proprietary technology, inventions, and other intellectual property that is commercially important to the development of our business by a variety of means, such as seeking, maintaining, and defending patent rights, whether developed internally or licensed from third parties. We also may rely on trade secrets and know-how relating to our proprietary technology platform, on continuing technological innovation and on in-licensing opportunities to develop, strengthen and maintain the strength of our position in the field of cell therapy that may be important for the development of our business. We also intend to seek patent protection or rely upon trade secret rights to protect other technologies that may be used to discover and validate targets, as well as to manufacture and develop novel cell therapy products. Additional regulatory protection may also be afforded through data exclusivity, market exclusivity and patent term extensions where available.

We are pursuing patent applications in both the US and abroad directed to our manufacturing process, including devices and methods for isolating TILs and expansion of cell populations. The earliest of these patent applications, if issued, would expire in 2038, without taking into account any possible patent term adjustment or extension. We are also pursuing patent applications in the U.S. and abroad as to indication-specific methods of treatment and our modified TIL program, including receptors providing targeted costimulation for adoptive cell therapy.

Government Regulation

The FDA and other regulatory authorities at federal, state, and local levels, as well as in foreign countries, extensively regulate, among other things, the research, development, testing, manufacture, quality control, import, export, safety, effectiveness, labeling, packaging, storage, distribution, record keeping, approval, advertising, promotion, marketing, post-approval monitoring, and post-approval reporting of biologics such as those we are developing. We, along with third-party contractors, will be required to navigate the various preclinical, clinical and commercial approval requirements of the governing regulatory agencies of the countries in which we wish to conduct studies or seek approval or licensure of our product candidates. The process of obtaining regulatory approvals and the subsequent compliance with applicable federal, state, local and foreign statutes and regulations require the expenditure of substantial time and financial resources.

U.S. Biologics Regulation

In the United States, biological products are subject to regulation under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, and other federal, state, local and foreign statutes and regulations. The process required by the FDA before biologics may be marketed in the United States generally involves the following:

- completion of preclinical laboratory tests and animal studies performed in accordance with the FDA's Good Laboratory Practice requirements, or GLP);
- submission to the FDA of an IND, which must become effective before clinical trials may begin;
- approval by an institutional review board, or IRB, or ethics committee at each clinical site before the trial is commenced;
- performance of adequate and well-controlled human clinical trials according to the FDA's regulations commonly referred to as good clinical practice, or GCP, regulations and any additional requirements for the protection of human research subjects and their health information to establish the safety, purity and potency of the proposed biologic product candidate for its intended purpose;
- preparation of and submission to the FDA of a BLA, after completion of all pivotal clinical trials;
- a determination by the FDA within 60 days of its receipt of a BLA to file the application for review;
- satisfactory completion of an FDA pre-approval inspection of the manufacturing facility or facilities at which the proposed product is produced to assess compliance with current Good Manufacturing Practices, or cGMP, and to assure that the facilities, methods and controls are adequate to preserve the biological product's continued safety, purity and potency and, if applicable, to assess compliance with the FDA's

current Good Tissue Practice, or cGTP, requirements for the use of human cellular and tissue products, and of selected clinical investigation sites to assess compliance with Good Clinical Practices, or GCPs;

- satisfactory completion of an FDA Advisory Committee review, if applicable;
- potential FDA audit of the nonclinical and clinical study sites that generated the data in support of the BLA; and
- FDA review and approval of the BLA to permit commercial marketing of the product for particular indications for use in the United States.

Before testing any biological product candidate in humans, the product candidate enters the preclinical testing stage. Preclinical tests, also referred to as nonclinical studies, include laboratory evaluations of product chemistry, toxicity and formulation, as well as animal studies to assess the potential safety and activity of the product candidate. The conduct of the preclinical tests must comply with federal regulations and requirements including GLPs.

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 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 pharmacodynamic 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.

In addition to the submission of an IND to the FDA before initiation of a clinical trial in the United States, certain human clinical trials involving recombinant or synthetic nucleic acid molecules are subject to oversight of institutional biosafety committees, or IBCs, as set forth in the National Institutes of Health, or NIH, Guidelines for Research Involving Recombinant DNA Molecules, or the NIH Guidelines. Specifically, under the NIH Guidelines, supervision of human gene transfer trials includes evaluation and assessment by an IBC, a local institutional committee that reviews and oversees research utilizing recombinant or synthetic nucleic acid molecules at that institution. The IBC assesses the safety of the research and identifies any potential risk to public health or the environment, and such review may result in some delay before initiation of a clinical trial. While the NIH Guidelines are not mandatory unless the research in question is being conducted at or sponsored by institutions receiving NIH funding of recombinant or synthetic nucleic acid molecule research, many companies and other institutions not otherwise subject to the NIH Guidelines voluntarily follow them.

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. 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.

For purposes of BLA approval, human clinical trials are typically conducted in three sequential phases that may overlap or be combined:

- Phase 1—The investigational product 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.
- Phase 2—The investigational product 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 investigational product 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.

In some cases, the FDA may require, or companies may voluntarily pursue, additional clinical trials after a product is approved to gain more information about the product in the intended therapeutic indication, particularly for long-term safety follow-up. These so-called Phase 4 studies may also be made a condition to approval of the BLA.

Concurrent with clinical trials, companies may complete additional animal studies and develop additional information about the biological characteristics of the product candidate, and must 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, must develop methods for testing the identity, strength, quality and purity of the final product. Additionally, 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.

BLA Submission and Review by the FDA

Assuming successful completion of all required testing in accordance with all applicable regulatory requirements, the results of product development, nonclinical studies and clinical trials are submitted to the FDA as part of a BLA requesting approval to market the product for one or more indications. The BLA must include all relevant data available from preclinical and clinical studies, including negative or ambiguous results as well as positive findings, together with detailed information relating to the product’s chemistry, manufacturing, controls, and proposed labeling, among other things. Data can come from company-sponsored clinical studies intended to test the safety and effectiveness of a use of the product, or from a number of alternative sources, including studies initiated by independent investigators. The submission of a BLA requires payment of a substantial application user fee to the FDA, unless a waiver or exemption applies.

Within 60 days following submission of the application, the FDA reviews a BLA submitted to determine if it is substantially complete before the FDA accepts it for filing. The FDA may refuse to file any BLA that it deems incomplete or not properly reviewable at the time of submission and may request additional information. In this event, the BLA must be resubmitted with the additional information. Once a BLA has been accepted for filing, the FDA’s goal is to review standard applications within ten months after the filing date, or, if the application qualifies

for priority review, six months after the FDA accepts the application for filing. In both standard and priority reviews, the review process may also be extended by FDA requests for additional information or clarification. The FDA reviews a BLA to determine, among other things, whether a product is safe, pure and potent and the facility in which it is manufactured, processed, packed or held meets standards designed to assure the product's continued safety, purity and potency. The FDA may also convene an advisory committee to provide clinical insight on application review questions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions.

Before approving a BLA, 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. For a product candidate that is also a human cellular or tissue product, the FDA also will not approve the application if the manufacturer is not in compliance with cGTPs. These are FDA regulations that govern the methods used in, and the facilities and controls used for, the manufacture of human cells, tissues, and cellular and tissue based products, or HCT/Ps, which are human cells or tissue intended for implantation, transplant, infusion, or transfer into a human recipient. The primary intent of the GTP requirements is to ensure that cell and tissue based products are manufactured in a manner designed to prevent the introduction, transmission and spread of communicable disease. FDA regulations also require tissue establishments to register and list their HCT/Ps with the FDA and, when applicable, to evaluate donors through screening and testing. Additionally, before approving a BLA, the FDA will typically inspect one or more clinical sites to assure compliance with GCP. If the FDA determines that the application, manufacturing process or manufacturing facilities are not acceptable, it will outline the deficiencies in the submission and often will request additional testing or information. Notwithstanding the submission of any requested additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval.

After the FDA evaluates a BLA and conducts inspections of manufacturing facilities where the investigational product and/or its drug substance will be produced, the FDA may issue an approval letter or a Complete Response Letter, or CRL. An approval letter authorizes commercial marketing of the product with specific prescribing information for specific indications. A CRL will describe all of the deficiencies that the FDA has identified in the BLA, except that where the FDA determines that the data supporting the application are inadequate to support approval, the FDA may issue the CRL without first conducting required inspections, testing submitted product lots, and/or reviewing proposed labeling. In issuing the CRL, the FDA may recommend actions that the applicant might take to place the BLA in condition for approval, including requests for additional information or clarification. The FDA may delay or refuse approval of a BLA if applicable regulatory criteria are not satisfied, require additional testing or information and/or require post-marketing testing and surveillance to monitor safety or efficacy of a product.

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 BLA with a Risk Evaluation and Mitigation Strategy, or REMS, to ensure the benefits of the product outweigh its risks, or otherwise limit the scope of any approval. A REMS is a safety strategy implemented to manage a known or potential serious risk associated with a product 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 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.

Expedited Development and Review Programs

The FDA offers a number of expedited development and review programs for qualifying product candidates. For example, the Fast Track program is intended to expedite or facilitate the process for reviewing new products that 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. Specifically, new biological products 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 and the specific indication for which it is being studied. The sponsor of a new biologic may request that the FDA designate the biologic as a Fast Track product at any time during the clinical development of the product. The sponsor of a Fast Track product has opportunities for more frequent interactions with the applicable FDA review team during product development and, once a BLA is submitted, the product candidate may be eligible for priority review. A Fast Track product may also be eligible for rolling review, where the FDA may consider for review sections of the BLA on a rolling basis before the complete application is submitted, if the sponsor provides a schedule for the submission of the sections of the BLA, the FDA agrees to accept sections of the BLA and determines that the schedule is acceptable, and the sponsor pays any required user fees upon submission of the first section of the BLA.

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 marketing application for a drug or biologic submitted to the FDA for approval, including a product candidate with a Fast Track designation and/or breakthrough therapy designation, may be eligible for other types of FDA programs intended to expedite development and review, such as priority review and accelerated approval. A product candidate is eligible for priority review if it has the potential to provide safe and effective therapy where no satisfactory alternative therapy exists or a significant improvement in the treatment, diagnosis or prevention of a disease compared to marketed products.. The FDA will attempt to direct additional resources to the evaluation of an application for a new biological product designated for priority review in an effort to facilitate the review. For original BLAs, priority review designation means the FDA's goal is to take action on the marketing application within six months of the 60-day filing date (as compared to ten months under standard review).

Additionally, product candidates studied for their safety and effectiveness in treating serious or life-threatening diseases or conditions may receive accelerated approval upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments. As a condition of accelerated approval, the FDA will generally require the sponsor to perform adequate and well-controlled post-marketing clinical studies 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 as a condition for accelerated approval pre-approval of promotional materials, which could adversely impact the timing of the commercial launch of the product.

Regenerative medicine advanced therapy, or RMAT, designation, is intended to facilitate an efficient development program for, and expedite review of, any drug or biologic that meets the following criteria: (i) the drug or biologic qualifies as a RMAT, which is defined as a cell therapy, therapeutic tissue engineering product, human cell and tissue product, or any combination product using such therapies or products, with limited exceptions; (ii) the drug or biologic is intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition; and

(iii) preliminary clinical evidence indicates that the drug or biologic has the potential to address unmet medical needs for such a disease or condition. RMAT designation provides all the benefits of breakthrough therapy designation, including more frequent meetings with the FDA to discuss the development plan for the product candidate and eligibility for rolling review and priority review. Product candidates granted RMAT designation may also be eligible for accelerated approval on the basis of a surrogate or intermediate endpoint reasonably likely to predict long-term clinical benefit, or reliance upon data obtained from a meaningful number of clinical trial sites, including through expansion of trials to additional sites. RMAT-designated products that receive accelerated approval may, as appropriate, fulfill their post-approval requirements through submission of clinical evidence, clinical studies, patient registries, or other sources of real-world evidence (such as electronic health records); through the collection of larger confirmatory data sets; or via post-approval monitoring of all patients treated with such therapy prior to approval of such therapy.

Fast Track designation, breakthrough therapy designation, priority review, accelerated approval, and RMAT designation do not change the standards for approval but may expedite the development or approval process. Even if a product candidate 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.

Orphan Drug Designation and Exclusivity

Under the Orphan Drug Act, the FDA may grant orphan designation to a drug or biologic intended to treat a rare disease or condition, defined as a disease or condition with a patient population of fewer than 200,000 individuals in the United States, or a patient population greater than 200,000 individuals in the United States and when there is no reasonable expectation that the cost of developing and making available the drug or biologic in the United States will be recovered from sales in the United States for that drug or biologic. Orphan drug designation must be requested before submitting a BLA. After the FDA grants orphan drug designation, the generic identity of the therapeutic agent and its potential orphan use are disclosed publicly by the FDA. Orphan drug designation does not convey any advantage in or shorten the duration of the regulatory review and approval process.

In the United States, orphan drug designation entitles a party to financial incentives such as opportunities for grant funding towards clinical trial costs, tax advantages and user-fee waivers. In addition, if a product that has orphan drug designation subsequently receives the first FDA approval for a particular drug or biologic for the disease 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, including a full BLA, to market the same biologic for the same indication for seven years, except in limited circumstances, such as a showing of clinical superiority to the product with orphan drug exclusivity or if the FDA finds that the holder of the orphan drug exclusivity has not shown that it can assure the availability of sufficient quantities of the orphan drug to meet the needs of patients with the disease or condition for which the drug was designated. Orphan drug exclusivity does not prevent the FDA from approving a different drug or biologic for the same disease or condition, or the same drug or biologic for a different disease or condition. Orphan product exclusivity also could block the approval of one of our products for seven years if a competitor obtains approval of the same biological product as defined by the FDA or if our product candidate is determined to be contained within the competitor’s product for the same indication or disease.

A designated orphan drug may not receive orphan drug exclusivity if it is approved for a use that is broader than the indication for which it received orphan designation. In addition, orphan drug exclusive marketing rights in the United States may be lost if the FDA later determines that the request for designation was materially defective or, as noted above, if a second applicant demonstrates that its product is clinically superior to the approved product with orphan exclusivity or the manufacturer of the approved product is unable to assure sufficient quantities of the product to meet the needs of patients with the rare disease or condition.

Post-Approval Requirements

Biologics 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. Biologic manufacturers and other entities involved in the manufacture and distribution of approved biological products 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 requirements and other laws. Accordingly, manufacturers must continue to expend time, money, and effort in the area of production and quality control to maintain GMP compliance. Changes to the manufacturing process or facility 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. 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 biologics. 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. FDA sanctions could include refusal to approve pending applications, withdrawal of an approval, clinical hold, warning or untitled letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, mandated corrective advertising or communications with doctors, debarment, restitution, disgorgement of profits, or civil or 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 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.

Government Regulation Outside of the United States

In addition to regulations in the United States, we will be subject to a variety of regulations in other jurisdictions governing, among other things, clinical studies and any commercial sales and distribution of our products. Because biologically sourced raw materials are subject to unique contamination risks, their use may be restricted in some countries. Whether or not we obtain FDA approval for a product, we must obtain the requisite approvals from regulatory authorities in foreign countries prior to the commencement of clinical studies or marketing of the product in those countries. Certain countries outside of the United States have a similar process that requires the submission of a clinical study application much like the IND prior to the commencement of human clinical studies.

In the European Union, for example, a clinical trial application, or CTA, must be submitted to each country's national health authority and an independent ethics committee, much like the FDA and the IRB, respectively. Once the CTA is approved in accordance with the applicable requirements, clinical study development may proceed. The requirements and process governing the conduct of clinical studies, are to a significant extent harmonized at the European Union-level but could vary from country to country. In all cases, the clinical studies are conducted in accordance with Good Clinical Practices, or GCP, and the applicable regulatory requirements and the ethical principles that have their origin in the Declaration of Helsinki. The way clinical trials are conducted in the European Union will undergo a major change when the Clinical Trial Regulation (Regulation (EU) No 536/2014) comes into application, probably in 2022. The Regulation harmonizes the assessment and supervision processes for clinical trials throughout the European Union via a Clinical Trials Information System, which will contain a centralized European Union portal and database.

To obtain regulatory approval of an investigational biological product under European Union regulatory systems, we must submit a marketing authorization application. The application used to file the BLA in the United States is similar to that required in the European Union, with the exception of, among other things, country-specific document requirements. Innovative products that target an unmet medical need may be eligible for a number of expedited development and review programs in the European Union, such as the PRIME scheme, which provides incentives similar to the breakthrough therapy designation in the United States. Such products are generally eligible for accelerated assessment and may also benefit from different types of Fast Track approvals, such as a conditional marketing authorization or a marketing authorization under exceptional circumstances granted on the basis of less comprehensive clinical data than normally required (respectively in the likelihood that the sponsor will provide such data within an agreed timeframe or when comprehensive data cannot be obtained even after authorization).

The European Union also provides opportunities for market exclusivity. For example, in the European Union, upon receiving marketing authorization, new chemical entities generally receive eight years of data exclusivity and an additional two years of market exclusivity. If granted, data exclusivity prevents regulatory authorities in the European Union from referencing the innovator's data to assess a generic or biosimilar application. During the additional two-year period of market exclusivity, a generic or biosimilar marketing authorization can be submitted, and the innovator's data may be referenced, but no generic or biosimilar product can be marketed until the expiration of the market exclusivity. However, there is no guarantee that a product will be considered by the European Union's regulatory authorities to be a new chemical entity, and products may not qualify for data exclusivity. Products receiving orphan designation in the European Union can receive ten years of market exclusivity, during which time no similar medicinal product for the same indication may be placed on the market. An orphan product can also obtain an additional two years of market exclusivity in the European Union for pediatric studies. No extension to any supplementary protection certificate can be granted on the basis of pediatric studies for orphan indications.

The criteria for designating an "orphan medicinal product" in the European Union are similar in principle to those in the United States. Under Article 3 of Regulation (EC) 141/2000, a medicinal product may be designated as orphan if (1) it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition; (2) either (a) such condition affects no more than five in 10,000 persons in the European Union when the application is made, or (b) the product, without the benefits derived from orphan status, would not generate

sufficient return in the European Union to justify investment; and (3) there exists no satisfactory method of diagnosis, prevention or treatment of such condition authorized for marketing in the European Union, or if such a method exists, the product will be of significant benefit to those affected by the condition, as defined in Regulation (EC) 847/2000. Orphan medicinal products are eligible for financial incentives such as reduction of fees or fee waivers and are, upon grant of a marketing authorization, entitled to ten years of market exclusivity for the approved therapeutic indication. The application for orphan drug designation must be submitted before the application for marketing authorization. The applicant will receive a fee reduction for the marketing authorization application if the orphan drug designation has been granted, but not if the designation is still pending at the time the marketing authorization is submitted. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process.

The 10-year market exclusivity may be reduced to six years if, at the end of the fifth year, it is established that the product no longer meets the criteria for orphan designation, for example, if the product is sufficiently profitable not to justify maintenance of market exclusivity. Additionally, marketing authorization may be granted to a similar product for the same indication at any time if:

- The second applicant can establish that its product, although similar, is safer, more effective or otherwise clinically superior;
- The applicant consents to a second orphan medicinal product application; or
- The applicant cannot supply enough orphan medicinal product.

The medicinal products we are developing, which are based on genes, cells or tissues, may be considered advanced therapy medicinal products, or ATMPs, in the European Union if they meet the scientific criteria for defining an ATMP. The principles of the aforementioned medicines legislation apply to ATMPs. All ATMPs must obtain a marketing authorization from the EMA and are regulated through the centralized authorization procedure. Regulation (EC) No 1394/2007, or the ATMP Regulation, provides specific incentives to accelerate the development of such products, including fee reductions for scientific advice, an ATMP classification procedure (for all developers) and a certification procedure for quality and non-clinical data (for SMEs only).

If tissues and cells are being used as starting materials in a medicinal product we may also need to comply with the requirements of Directive 2004/23/EC, or the European Tissues and Cells Directive, covering standards for donation, procurement and testing, processing, preservation, storage and distribution of human tissues and cells, as well as its technical implementing directives; and Directive 2015/566, as regards the procedures for verifying the equivalent standards of quality and safety of imported tissues and cells.

In the European Union, early access mechanisms for innovative medicines (such as compassionate use programs and named patient supplies), pricing and reimbursement, and promotion and advertising are subject to national regulations and oversight by national competent authorities and therefore significantly vary from country to country.

Sanctions for non-compliance with the aforementioned requirements, which may include administrative and criminal penalties, are generally determined and enforced at national level. However, under the European Union financial penalties regime, the EMA can investigate and report on alleged breaches of the European Union pharmaceutical rules by holders of a marketing authorization for centrally authorized medicinal products and the European Commission could adopt decisions imposing significant financial penalties on infringing marketing authorization holders.

The United Kingdom has left the European Union on January 31, 2020. Following the Transition Period which ended on December 31, 2020, Brexit could materially impact the regulatory regime with respect to the development, manufacture, importation, approval and commercialization of our product candidates in the United Kingdom in the coming years.

For other countries outside of the European Union, such as countries in Eastern Europe, Latin America or Asia, the requirements governing the conduct of clinical studies, product licensing, pricing and reimbursement vary from country to country. In all cases, again, the clinical studies are conducted in accordance with GCP and the applicable regulatory requirements and the ethical principles that have their origin in the Declaration of Helsinki.

If we fail to comply with applicable foreign regulatory requirements, we may be subject to, among other things, fines, suspension or withdrawal of regulatory approvals, product recalls, seizure of products, operating restrictions and criminal prosecution.

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 and may constrain the financial arrangements and relationships through which we research, as well as, sell, market and distribute any products for which we obtain marketing approval. Such laws include, without limitation, federal and state anti-kickback, fraud and abuse, false claims, data privacy and security and physician and other health care provider transparency laws and regulations. The laws that will affect our operations include, but are not limited to:

- the federal Anti-Kickback Statute , which prohibits, among other things, persons from knowingly and willfully soliciting, offering, receiving or providing remuneration (including any kickback, bribe or rebate), directly or indirectly, in cash or in kind, to induce or reward either the referral of an individual for, or the purchase, order or recommendation of, any good or service for which payment may be made under federal and state healthcare programs such as Medicare and Medicaid;
- federal civil and criminal false claims laws and civil monetary penalty laws, including the federal False Claims Act, impose criminal or civil penalties, as applicable, against individuals or entities for knowingly presenting, or causing to be presented, to the federal government (including the Medicare and Medicaid programs) or other third-party payor claims for payment that are false or fraudulent or making a false statement to avoid, decrease or conceal an obligation to pay money to the federal government;
- Health Insurance Portability and Accountability Act of 1996, or HIPAA established the federal offense of health care fraud, which among other things, imposes criminal liability for knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program or to obtain, by means of false or fraudulent pretenses, representations, or promises, any of the money or property owned by, or under the custody or control of, any healthcare benefit program, regardless of the payor (e.g. public or private) and knowingly and willfully falsifying, concealing or covering up by any trick or device a material fact or making any materially false statements in connection with the delivery of or payment for healthcare benefits, items or services relating to healthcare matters;
- HIPAA, as amended by Health Information Technology for Economic and Clinical Health Act , or HITECH, and its implementing regulations, which imposes certain obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information without the appropriate authorization by entities subject to the law, such as health plans, healthcare clearinghouses and healthcare providers and their respective business associates and their covered subcontractors;
- the federal the Physician Payments Sunshine Act and its implementing regulations, requires applicable group purchasing organizations and manufacturers of drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program (with certain exceptions) to report annually to HHS information related to "payments or other transfers of value" made in the previous year to covered recipients, including physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors, other health care professionals (such as nurse practitioners and physician assistants) and teaching hospitals, and information regarding ownership and investment interests held by physicians (as defined above) or their immediate family members; and

- analogous state and foreign laws and regulations, including: state anti-kickback and false claims laws that may apply to our business practices (including research, distribution, sales and marketing arrangements and claims involving healthcare items or services reimbursed by state governmental and non-governmental third-party payors, including private insurers); state laws that require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the applicable compliance guidance promulgated by the federal government; state laws that require drug manufacturers to track gifts and other remuneration and items of value provided to healthcare professionals and entities and file reports relating to pricing and marketing information; and state and foreign laws that govern the privacy and security of health information in specified circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

Because of the breadth of these laws and the narrowness of any available statutory exceptions and safe harbors, it is possible that some of our current and future business activities could be subject to challenge under one or more of such laws.

If our significant operations are found to be in violation of any of such laws or any other governmental regulations that apply, they may be subject to penalties, including, without limitation, administrative, civil and criminal penalties, damages, fines, disgorgement, the curtailment or restructuring of operations, integrity oversight and reporting obligations, exclusion from participation in federal and state healthcare programs and imprisonment.

Coverage and Reimbursement

Sales of any 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. Decisions regarding the extent of coverage and amount of reimbursement to be provided are made on a plan-by-plan basis. These third-party payors are increasingly reducing coverage and reimbursement for medical products, drugs and services. In addition, the U.S. government, state legislatures and foreign governments have continued implementing cost-containment programs, including price controls, restrictions on coverage and reimbursement and requirements for substitution of generic products. 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 and also have a material adverse effect on sales.

Healthcare Reform

In the United States, in March 2010, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, each as amended, collectively known as the ACA, was enacted, which substantially changed the way healthcare is financed by both governmental and private insurers, and significantly affected the pharmaceutical industry. The ACA contained a number of provisions, including those governing enrollment in federal healthcare programs, reimbursement adjustments and changes to fraud and abuse laws. For example, 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;
- required manufacturers to participate in a coverage gap discount program, under which they must agree to offer 70 percent 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; and

- imposed a non-deductible annual fee on pharmaceutical manufacturers or importers who sell “branded prescription drugs” to specified federal government programs.

Since its enactment, there have been judicial and Congressional challenges to certain aspects of the ACA. For example, on June 17, 2021, the U.S. Supreme Court dismissed the most recent judicial challenge to the ACA brought by several states without specifically ruling on the constitutionality of the ACA. Prior to the Supreme Court’s decision, President Biden issued an executive order that initiated a special enrollment period 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, including among others, reexamining Medicaid demonstration projects and waiver programs that include work requirements, and policies that create unnecessary barriers to obtaining access to health insurance coverage through Medicaid or the ACA. 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, which was temporarily suspended from May 1, 2020 through March 31, 2022 due to the COVID-19 pandemic, and reduced payments to several types of Medicare providers. Under current legislation the actual reduction in Medicare payments will vary from 1% in 2022 to up to 3% in the final fiscal year of this sequester. Additionally, on March 11, 2021, President Biden signed the American Rescue Plan Act of 2021 into law, which eliminates the statutory Medicaid drug rebate cap, currently set at 100% of a drug’s average manufacturer price, for single source and innovator multiple source drugs, beginning January 1, 2024. Moreover, there has recently been heightened governmental scrutiny over the manner in which manufacturers set prices for their marketed products, which has resulted in several Congressional inquiries, proposed and enacted legislation and executive orders issued by the President designed to, among other things, bring more transparency to product pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for drug products. It is also possible that additional governmental action is taken in response to the COVID-19 pandemic. In July 2021, the Biden administration released an executive order, “Promoting Competition in the American Economy,” with multiple provisions aimed at prescription drugs. In response to Biden’s executive order, on September 9, 2021, HHS released a Comprehensive Plan for Addressing High Drug Prices that outlines principles for drug pricing reform and sets out a variety of potential legislative policies that Congress could pursue to advance these principles. No legislation or administrative actions have been finalized to implement these principles. In addition, Congress is considering drug pricing as part of other reform initiatives. Similar reform measures are been considered and adopted at the state level as well.

Individual states in the United States have also become increasingly active in implementing regulations designed to control pharmaceutical product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing.

Facilities

We control and operate our manufacturing site in Manchester, United Kingdom, which consists of 12,957 total square feet of leased laboratory and office space under eight leases that expire in July 2022, January 2023, and July 2024. We own and are developing our manufacturing facility in Tarzana, California, which has 102,607 square feet of clinical and manufacturing space, and lease 6,000 square feet of office space in Tarzana, California. Our Tarzana clinical manufacturing facility is expected to become operational in the first half of 2022.

Our headquarters is currently located in Dallas, Texas and consists of 5,055 square feet of leased office space under a lease that expires in April 2026. We also lease 42,240 square feet of laboratory and office space in Thousand Oaks, California, under a lease that expires in October 2026, and 7,036 square feet of leased laboratory and office space in Alderley Park, United Kingdom, under two leases that expire in November 2025 and April 2026, which in each case is subject to renewal. Additionally, we lease laboratory and office space in other parts of the United States. We believe that our facilities are adequate for our current needs, and that suitable additional alternative spaces will be available in the future on commercially reasonable terms.

Employees and Human Capital Resources

As of December 31, 2021, we had 412 full-time employees. Of these employees, 352 were engaged in research and development activities and 68 held Ph.D. or M.D. degree. Substantially all of our employees are based in Dallas, Texas, greater Los Angeles, California and Manchester, United Kingdom. None of our employees are represented by labor unions or covered by collective bargaining agreements. We consider our relationship with our employees to be good.

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

Legal Proceedings

From time to time, we may become involved in legal proceedings arising in the ordinary course of our business. We are not currently subject to any material legal proceedings.

Corporate Information

We were incorporated under the laws of the State of Delaware in August of 2018. Our principal executive offices are located at 3963 Maple Avenue, Suite 350, Dallas, Texas 75219 and our telephone number is (972) 499-3350. Our website address is instilbio.com. The information contained on, or accessible through, our website is not incorporated by reference into this prospectus, and you should not consider any information contained in, or that can be accessed through, our website as part of this prospectus or in deciding whether to purchase our common stock. We have included our website in this prospectus solely as an inactive textual reference.

Available Information

Annual Reports on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K, and amendments to reports filed pursuant to Sections 13(a) and 15(d) of the Securities Exchange Act of 1934, as amended, or the Exchange Act, will be made available free of charge on our website as soon as reasonably practicable after we electronically file such material with, or furnish it to, the Securities and Exchange Commission, or SEC. The contents of our website are not incorporated into this Annual Report and our reference to the URL for our website is intended to be an inactive textual reference only. The information contained on, or that can be accessed through, our website is not a part of this document.

Item 1A. Risk Factors.

RISK FACTORS

The following information sets forth risk factors that could cause our actual results to differ materially from those contained in forward-looking statements we have made in this Annual Report on Form 10-K and those we may make from time to time. You should carefully consider the risks described below, in addition to the other information contained in this Annual Report on Form 10-K and our other public filings. Our business, financial condition or results of operations could be harmed by any of these risks. The risks and uncertainties described below are not the only ones we face. Additional risks not presently known to us or other factors not perceived by us to present significant risks to our business at this time also may impair our business operations.

Risks Associated with Our Business

Our business is subject to a number of risks of which you should be aware before making a decision to invest in our common stock. These risks are more fully described in this “Risk Factors” section, including the following:

- We have incurred significant losses since our inception. We expect to incur losses over the next several years and may never achieve or maintain profitability.
- We have a limited operating history and no history of commercializing products, which may make it difficult for an investor to evaluate the success of our business to date and to assess our future viability.
- We will need substantial additional funding to meet our financial obligations and to pursue our business objectives. If we are unable to raise capital when needed, we could be forced to curtail our planned operations and the pursuit of our growth strategy.
- All of our product candidates are currently in clinical and preclinical development. If we are unable to successfully develop, receive regulatory approval for and commercialize our product candidates for the indications we seek, or successfully develop any other product candidates, or experience significant delays in doing so, our business will be harmed.
- Because ITIL-168, as well as ITIL-306 and any future product candidates developed from our CoStAR platform, represent novel approaches to the treatment of disease, there are many uncertainties regarding the development, market acceptance, third-party reimbursement coverage and commercial potential of our product candidates.
- The regulatory approval processes of the FDA, EMA and comparable foreign authorities are lengthy, time consuming and inherently unpredictable. If we are not able to obtain required regulatory approval for our product candidates, our business will be substantially harmed.
- Success in preclinical studies or earlier clinical trials, including our compassionate use program, may not be indicative of results in future clinical trials. Our product candidates may not have favorable results in later clinical trials, if any, or receive regulatory approval.
- Negative public opinion of TIL therapies and increased regulatory scrutiny of cell therapy using TILs may adversely impact the development or commercial success of our current and future product candidates.
- As an organization, we are early in the process of conducting our first clinical trial, have no prior experience in conducting clinical trials, and may be unable to do so for any product candidates we may develop, including ITIL-168. Further, the FDA, EMA or other foreign regulatory authorities may require us to obtain and submit additional nonclinical data supporting the comparability of ITIL-168 with the TIL product that was evaluated in the compassionate use program in the United Kingdom that was manufactured using a prior version of the ITIL-168 manufacturing process, or may not permit us to rely on the data from the compassionate use program to support the development of ITIL-168 at all, which could delay clinical development or marketing approval of ITIL-168
- We may not be successful in our efforts to build a pipeline of additional product candidates.
- Our business and operations may be adversely affected by the evolving and ongoing COVID-19 global pandemic.
- Cell therapies are complex and difficult to manufacture. We could experience manufacturing problems that result in delays in the development or commercialization of our product candidates or otherwise harm our business.
- The affected populations for our product candidates may be smaller than we or third parties currently project, which may affect the addressable markets for our product candidates.
- We face significant competition from other biotechnology and pharmaceutical companies, and our operating results will suffer if we fail to compete effectively.
- If we are unable to obtain or protect intellectual property rights related to any of our product candidates, we may not be able to compete effectively in our market.

- Third parties may initiate legal proceedings alleging that we are infringing their intellectual property rights, the outcome of which would be uncertain.

Risks Related to our Financial Position and Capital Needs

We have incurred significant losses since our inception. We expect to incur losses over the next several years and may never achieve or maintain profitability.

Since our inception, we have incurred significant net losses, and we expect to continue to incur significant expenses and operating losses for the foreseeable future. Our net losses were $156.8 million and $37.7 million for the years ended December 31, 2021 and 2020, respectively. As of December 31, 2021, we had an accumulated deficit of $201.7 million. Since 2019, we have financed our operations with $719.0 million in net proceeds raised in our initial public offering and private placements of convertible preferred stock to date. We have no products approved for commercialization and have never generated any revenue from product sales.

All of our product candidates are still in clinical and preclinical testing. We expect to continue to incur significant expenses and operating losses over the next several years. We expect that it could be several years, if ever, before we have a commercialized product. Our net losses may fluctuate significantly from quarter to quarter and year to year. We anticipate that our expenses will increase substantially as we:

- conduct our ongoing clinical trial of ITIL-168 and planned clinical trial of ITIL-306, as well as initiate and complete additional clinical trials of future product candidates or current product candidates in new indications;
- continue to advance the preclinical and clinical development of our product candidates and our preclinical and discovery programs, including in our CoStAR platform;
- seek regulatory approval for any product candidates that successfully complete clinical trials;
- continue to develop our product candidate pipeline;
- scale up our clinical and regulatory capabilities;
- manufacture current good manufacturing practices, or cGMP, material for clinical trials or potential commercial sales at our manufacturing facilities;
- establish and validate a commercial-scale cGMP manufacturing facility;
- establish a commercialization infrastructure and scale up internal and external manufacturing and distribution capabilities to commercialize any product candidates for which we may obtain regulatory approval;
- adapt our regulatory compliance efforts to incorporate requirements applicable to marketed products;
- maintain, expand and protect our intellectual property portfolio;
- hire additional clinical, manufacturing quality control, regulatory, manufacturing and scientific and administrative personnel;
- add operational, financial and management information systems and personnel, including personnel to support our product development and planned future commercialization efforts; and
- incur additional legal, accounting and other expenses in operating as a public company.

To date, we have not generated any revenue from product sales. To become and remain profitable, we must succeed in developing and eventually commercializing product candidates that generate significant revenue. This will require us to be successful in a range of challenging activities, including completing preclinical testing and clinical trials of our product candidates, obtaining regulatory approval, and manufacturing, marketing and selling any product candidates for which we may obtain regulatory approval, as well as discovering and developing additional product candidates. We are only in the preliminary stages of most of these activities and all of our product

candidates are in clinical or preclinical development. We may never succeed in these activities and, even if we do, may never generate any revenue or revenue that is significant enough to achieve profitability.

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

We have a limited operating history and no history of commercializing products, which may make it difficult for an investor to evaluate the success of our business to date and to assess our future viability.

We are a clinical-stage biopharmaceutical company with a limited operating history. We commenced operations in 2019, and our operations to date have been largely focused on organizing and staffing our company, business planning, raising capital, acquiring our technology and product candidates, acquiring our facilities in Tarzana, California, developing our manufacturing capabilities and developing our clinical and preclinical product candidates, including undertaking preclinical studies and conducting clinical trials. To date, we have not yet demonstrated our ability to successfully complete pivotal clinical trials, obtain regulatory approvals, manufacture a product on a commercial scale, or arrange for a third party to do so on our behalf, or conduct sales and marketing activities necessary for successful commercialization. Consequently, any predictions you make 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 products.

We may encounter unforeseen expenses, difficulties, complications, delays and other known or unknown factors in achieving our business objectives. We will need to develop commercial capabilities, and we may not be successful in doing so.

We will need substantial additional funding to meet our financial obligations and to pursue our business objectives. If we are unable to raise capital when needed, we could be forced to curtail our planned operations and the pursuit of our growth strategy.

Our operations have consumed substantial amounts of cash since inception. Identifying and acquiring potential product candidates, conducting preclinical testing and clinical trials and developing manufacturing operations for our product candidates is a time-consuming, expensive and uncertain process that takes years to complete, and we may never generate the necessary data or results required to obtain regulatory approval and achieve product sales. We expect to continue to incur significant expenses and operating losses over the next several years as we conduct clinical trials of our product candidates, initiate future clinical trials of our product candidates, advance our preclinical programs, build our manufacturing capabilities, seek marketing approval for any product candidates that successfully complete clinical trials and advance any of our other product candidates we may develop or otherwise acquire. In addition, our product candidates, if approved, may not achieve commercial success. Our revenue, if any, will be derived from sales of products that we do not expect to be commercially available for a number of years, if at all. If we obtain marketing approval for any product candidates that we develop or otherwise acquire, we expect to incur significant commercialization expenses related to product sales, marketing, distribution and manufacturing. We also expect an increase in our expenses associated with creating additional infrastructure to support operations as a public company. Accordingly, we will need to obtain substantial additional funding in order to continue our operations.

As of December 31, 2021, we had cash, cash equivalents, restricted cash, and marketable securities of $454.6 million, which consists of $37.6 million in cash and cash equivalents, $0.5 million in restricted cash, and $416.5 million in marketable securities. We believe that our existing cash, cash equivalents and marketable securities will be sufficient to fund our operating expenses and capital requirements into 2023. This estimate is based on assumptions that may prove to be wrong, and we could use our available capital resources sooner than we expect. Changes may occur beyond our control that would cause us to consume our available capital before that time,

including changes in and progress of our development activities, acquisitions of additional product candidates, and changes in regulation. Our future capital requirements will depend on many factors, including:

- the scope, progress, costs and results of discovery, preclinical development, laboratory testing and clinical trials for ITIL-168, ITIL-306 and future product candidates;
- the extent to which we develop, in-license or acquire other product candidates and technologies in our product candidate pipeline;
- the costs and timing of process development and manufacturing scale-up activities associated with our product candidates and other programs as we advance them through preclinical and clinical development;
- the number and development requirements of product candidates that we may pursue;
- the costs, timing and outcome of regulatory review of our product candidates;
- our headcount growth and associated costs as we expand our research and development capabilities and establish a commercial infrastructure;
- the costs of establishing and maintaining our own commercial-scale cGMP manufacturing facility;
- the costs and timing of future commercialization activities, including product manufacturing, marketing, sales, and distribution, for any of our product candidates for which we receive marketing approval;
- the costs and timing of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending any intellectual property-related claims;
- the revenue, if any, received from commercial sales of our product candidates for which we receive marketing approval; and
- the costs of operating as a public company.

We will require additional capital to achieve our business objectives. Additional funds may not be available on a timely basis, on favorable terms, or at all, and such funds, if raised, may not be sufficient to enable us to continue to implement our long-term business strategy. Further, our ability to raise additional capital may be adversely impacted by potential worsening global economic conditions and the recent disruptions to and volatility in the credit and financial markets in the United States and worldwide resulting from the ongoing COVID-19 pandemic. If we are unable to raise sufficient additional capital, we could be forced to curtail our planned operations and the pursuit of our growth strategy.

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 substantial revenue, we may finance our cash needs through a combination of equity offerings, government or private party grants, debt financings and license and collaboration agreements. We do not currently have any other committed external source of funds. To the extent that we raise additional capital through the sale of equity or convertible debt securities, your ownership interest 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 collaborations, strategic alliances or marketing, distribution or licensing arrangements with third parties, we may be required to relinquish valuable rights to our technologies, future revenue streams or product candidates, grant licenses on terms that may not be favorable to us or commit to future payment streams. 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 or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

Risks Related to the Development of our Product Candidates

All of our product candidates are currently in clinical and preclinical development. If we are unable to successfully develop, receive regulatory approval for and commercialize our product candidates for the indications we seek, or successfully develop any other product candidates, or experience significant delays in doing so, our business will be harmed.

We currently have no products approved for commercial sale, and all of our product candidates are currently in clinical and preclinical development. To date, we have clinical experience in the context of a compassionate use program at a single clinical site with a TIL product that was manufactured using a prior version of the ITIL-168 manufacturing process. However, as an organization, we are early in the process of conducting our first multi-center clinical trial with centralized manufacturing, have no prior experience in conducting any clinical trials, have limited experience in preparing, submitting and prosecuting regulatory filings and have not previously submitted a BLA for any product candidate. Each of our programs and product candidates will require additional preclinical and/or clinical development, regulatory approval, obtaining manufacturing supply, capacity and expertise, building a commercial organization or successfully outsourcing commercialization, substantial investment and significant marketing efforts before we generate any revenue from product sales. We do not have any products that are approved for commercial sale, and we may never be able to develop or commercialize marketable products.

Our ability to generate revenue from our product candidates, which we do not expect will occur for several years, if ever, will depend heavily on the successful development, regulatory approval and eventual commercialization of our product candidates. The success of ITIL-168, ITIL-306 or any other product candidates that we develop or otherwise may acquire will depend on several factors, including:

- timely and successful completion of preclinical studies and clinical trials;
- effective investigational new drug applications, or INDs, from the U.S. Food and Drug Administration (FDA), or comparable foreign applications that allow commencement of our planned clinical trials or future clinical trials for our product candidates;
- sufficiency of our financial and other resources to complete the necessary preclinical studies and clinical trials;
- successful enrollment and completion of clinical trials, including under the FDA's current Good Clinical Practices, or GCPs, and current Good Laboratory Practices;
- successful development of, or making arrangements with third-party manufacturers for, our commercial manufacturing processes for any of our product candidates that receive regulatory approval;
- receipt of timely marketing approvals from applicable regulatory authorities;
- launching commercial sales of products, if approved, whether alone or in collaboration with others;
- acceptance of the benefits and use of our products, including method of administration, if approved, by patients, the medical community and third-party payors, for their approved indications;
- the prevalence and severity of adverse events experienced with ITIL-168, ITIL-306 or any other product candidates;
- the availability, perceived advantages, cost, safety and efficacy of alternative therapies for any product candidate, and any indications for such product candidate, that we develop;
- our ability to produce ITIL-168, ITIL-306 or any other product candidates we develop on a commercial scale;

- obtaining and maintaining patent, trademark and trade secret protection and regulatory exclusivity for our product candidates and otherwise protecting our rights in our intellectual property portfolio;
- maintaining compliance with regulatory requirements, including cGMPs, and complying effectively with other procedures;
- obtaining and maintaining third-party coverage and adequate reimbursement and patients' willingness to pay out-of-pocket in the absence of such coverage and adequate reimbursement; and
- maintaining a continued acceptable safety, tolerability and efficacy profile of the products following approval.

If we are not successful with respect to one or more of these factors in a timely manner or at all, we could experience significant delays or an inability to successfully commercialize the product candidates we develop, which would materially harm our business. If we do not receive marketing approvals for any product candidate we develop, we may not be able to continue our operations.

Because ITIL-168, as well as ITIL-306 and any future product candidates developed from our CoStAR platform, represent novel approaches to the treatment of disease, there are many uncertainties regarding the development, market acceptance, third-party reimbursement coverage and commercial potential of our product candidates.

Human immunotherapy products are a new category of therapeutics, and to date, no TIL therapies have been approved by the FDA, EMA or other foreign regulatory authorities. Because this is a relatively new and expanding area of novel therapeutic interventions, there are many uncertainties related to development, marketing, reimbursement and the commercial potential for our product candidates. There can be no assurance as to the length of the trial period, the number of patients the FDA will require to be enrolled in the trials in order to establish the safety, efficacy, purity and potency of immunotherapy products or that the data generated in these trials will be acceptable to the FDA to support marketing approval. The FDA may take longer than usual to come to a decision on any biologics license application, or BLA, that we submit and may ultimately determine that there is not enough data, information, or experience with our product candidates to support an approval decision. The FDA may also require that we conduct additional post-marketing studies or implement risk management programs, such as Risk Evaluation and Mitigation Strategies, or REMS, until more experience with our product candidates is obtained. Finally, after increased usage, we may find that our product candidates do not have the intended effect or have unanticipated side effects, potentially jeopardizing initial or continuing regulatory approval and commercial prospects.

The success of our business depends in part upon our ability to develop engineered TIL therapies using our CoStAR platform. The CoStAR platform is novel and we have not yet initiated or completed a clinical trial of any product candidate developed using the CoStAR platform. The platform may fail to deliver TIL therapies that are effective in the treatment of tumor types that have historically been resistant to immunotherapy. Even if we are able to identify and develop TIL therapies using the CoStAR platform, we cannot assure that such product candidates will achieve marketing approval to safely and effectively treat cancer.

If we uncover any previously unknown risks related to our CoStAR platform, or if we experience unanticipated problems or delays in developing our CoStAR product candidates, we may be unable to achieve our strategy of building a pipeline of TIL therapies.

We may also find that the manufacture of our product candidates is more difficult than anticipated, resulting in an inability to produce a sufficient amount of our product candidates for our clinical trials or, if approved, commercial supply. Moreover, because of the complexity and novelty of our manufacturing process, we may face difficulties in transferring the process from our facility in Manchester, United Kingdom to our new facility in Tarzana, California, which could hinder our ability to replicate our manufacturing to supply our clinical development or our commercial efforts.

There is no assurance that the approaches offered by our products will gain broad acceptance among doctors or patients or that governmental agencies or third-party medical insurers will be willing to provide reimbursement coverage for proposed product candidates. Since our current product candidates and any future product candidates will represent novel approaches to treating various conditions, it may be difficult, in any event, to accurately estimate the potential revenues from these product candidates. Accordingly, we may spend significant capital trying to obtain approval for product candidates that have an uncertain commercial market. The market for any products that we successfully develop will also depend on the cost of the product. We do not yet have sufficient information to reliably estimate what it will cost to commercially manufacture our current product candidates, and the actual cost to manufacture these products could materially and adversely affect the commercial viability of these products. Our goal is to reduce the cost of manufacturing and providing our product candidates. However, unless we can reduce those costs to an acceptable amount, we may never be able to develop a commercially viable product. If we do not successfully develop and commercialize products based upon our approach or find suitable and economical sources for materials used in the production of our products, we will not become profitable, which would materially and adversely affect the value of our common stock.

Our TIL therapies and our other therapies may be provided to patients in combination with other agents provided by third parties. The cost of such combination therapy may increase the overall cost of therapy and may result in issues regarding the allocation of reimbursements between our therapy and the other agents, all of which may affect our ability to obtain reimbursement coverage for the combination therapy from governmental or private third party medical insurers.

Preclinical studies and clinical trials are expensive, time-consuming, difficult to design and implement and involve an uncertain outcome. Further, we may encounter substantial delays in completing the development of our product candidates.

All of our product candidates are in clinical and preclinical development and their risk of failure is high. The clinical trials and manufacturing of our product candidates are, and the manufacturing and marketing of our products, if approved, will be, subject to extensive and rigorous review and regulation by numerous government authorities in the United States and in other countries where we intend to test and market our product candidates. Before obtaining regulatory approvals for the commercial sale of any of our product candidates, we must demonstrate through lengthy, complex and expensive preclinical testing and clinical trials that our product candidates are both safe and effective for use in each target indication. In particular, because our product candidates are subject to regulation as biological products, we will need to demonstrate that they are safe, pure and potent for use in their target indications. Each product candidate must demonstrate an adequate risk versus benefit profile in its intended patient population and for its intended use.

Clinical trials are expensive and can take many years to complete, and its outcome is inherently uncertain. We cannot guarantee that any clinical trials will be conducted as planned or completed on schedule, if at all. Failure can occur at any time during the clinical trial process. Even if our future clinical trials are completed as planned, we cannot be certain that their results will support the safety and effectiveness of our product candidates for their targeted indications or support continued clinical development of such product candidates. Our future clinical trial results may not be successful.

In addition, even if such trials are successfully completed, we cannot guarantee that the FDA, EMA or other foreign regulatory authorities will interpret the results as we do, and more trials could be required before we submit our product candidates for approval. Moreover, results acceptable to support approval in one jurisdiction may be deemed inadequate by another regulatory authority to support regulatory approval in that other jurisdiction. To the extent that the results of the trials are not satisfactory to the FDA, EMA or other 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.

To date, we have not completed any clinical trials required for the approval of our product candidates. We may experience delays in conducting any clinical trials and we do not know whether our clinical trials will begin on time, need to be redesigned, recruit and enroll patients on time or be completed on schedule, or at all. Clinical trials can be delayed suspended or terminated for a variety of reasons, including in connection with:

- inability to generate sufficient preclinical, toxicology, or other in vivo or in vitro data to support the initiation of clinical trials;
- delays in sufficiently developing, characterizing or controlling a manufacturing process suitable for advanced clinical trials;
- delays in developing suitable assays for screening patients for eligibility for trials with respect to certain product candidates;
- delays in reaching agreement with the FDA, EMA or other regulatory authorities as to the design or implementation of our clinical trials;
- obtaining regulatory authorization to commence a clinical trial;
- reaching an agreement on acceptable terms with clinical trial sites or prospective contract research organizations, or CROs, the terms of which can be subject to extensive negotiation and may vary significantly among different clinical trial sites;
- obtaining IRB approval at each trial site;
- recruiting suitable patients to participate in a clinical trial;
- having patients complete a clinical trial or return for post-treatment follow-up;
- inspections of clinical trial sites or operations by applicable regulatory authorities, or the imposition of a clinical hold;
- clinical sites, CROs or other third parties deviating from trial protocol or dropping out of a trial;
- failure to perform in accordance with the applicable regulatory requirements, including FDA's GCP requirements, or applicable regulatory requirements in other countries;
- addressing patient safety concerns that arise during the course of a trial, including occurrence of adverse events associated with the product candidate that are viewed to outweigh its potential benefits;
- adding a sufficient number of clinical trial sites;
- manufacturing sufficient quantities of product candidate for use in clinical trials; or
- suspensions or terminations by IRBs of the institutions at which such trials are being conducted, by the Data Safety Monitoring Board, or DSMB, for such trial or by the FDA or other regulatory authorities due to a number of factors, including those described above.

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

- we may experience changes in regulatory requirements or guidance, or receive feedback from regulatory authorities that requires us to modify the design of our clinical trials;
- clinical trials of our product candidates may produce negative or inconclusive results, and we may decide, or regulators may require us, to conduct additional clinical trials or abandon development programs;
- the number of patients required for clinical trials of our product candidates may be larger than we anticipate, enrollment in these clinical trials may be slower than we anticipate or participants may drop out of these clinical trials at a higher rate than we anticipate;
- our third-party contractors may fail to comply with regulatory requirements or meet their contractual obligations to us in a timely manner, or at all;

- we or our investigators might have to suspend or terminate clinical trials of our product candidates for various reasons, including non-compliance with regulatory requirements, a finding that our product candidates have undesirable side effects or other unexpected characteristics, or a finding that the participants are being exposed to unacceptable health risks;
- the cost of clinical trials of our product candidates may be greater than we anticipate and we may not have funds to cover the costs;
- the supply or quality of our product candidates or other materials necessary to conduct clinical trials of our product candidates may be insufficient or inadequate;
- regulators may revise the requirements for approving our product candidates, or such requirements may not be as we anticipate; and
- any future collaborators that conduct clinical trials may face any of the above issues, and may conduct clinical trials in ways they view as advantageous to them but that are suboptimal for us.

If we are required to conduct additional clinical trials or other testing of our product candidates beyond those that we currently contemplate, if we are unable to successfully complete clinical trials of our product candidates or other testing, if the results of these trials or tests are not positive or are only modestly positive or if there are safety concerns, we may:

- incur unplanned costs;
- be delayed in obtaining marketing approval for our product candidates or not obtain marketing approval at all;
- obtain marketing approval in some countries and not in others;
- obtain marketing approval for indications or patient populations that are not as broad as intended or desired;
- obtain marketing approval with labeling that includes significant use or distribution restrictions or safety warnings, including boxed warnings or REMS.
- be subject to additional post-marketing testing requirements;
- be subject to changes in the way the product is administered; or
- have regulatory authorities withdraw or suspend their approval of the product or to impose restrictions on its distribution after obtaining marketing approval.

We could encounter delays if a clinical trial is suspended or terminated by us, by the IRBs of the institutions in which such trials are being conducted, by the Data Safety Monitoring Board for such trial or by 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.

All of our product candidates will require extensive clinical testing before we are prepared to submit a BLA or marketing authorization application, or MAA, for regulatory approval. We cannot predict with any certainty if or when we might complete the clinical development for our product candidates and submit a BLA or MAA for regulatory approval of any of our product candidates or whether any such BLA or MAA will be approved. We may also seek feedback from the FDA, EMA or other regulatory authorities on our clinical development program, and the FDA, EMA or such regulatory authorities may not provide such feedback on a timely basis, or such feedback may not be favorable, which could further delay our development programs.

We cannot predict with any certainty whether or when we might complete a given clinical trial. If we experience delays in the commencement or completion of our clinical trials, or if we terminate a clinical trial prior to completion, the commercial prospects of our product candidates could be harmed, and our ability to generate revenues from our product candidates may be delayed or lost. In addition, any delays in our clinical trials could increase our costs, slow down 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.

We have received Fast Track designation for ITIL-168 for the treatment of metastatic melanoma, and we may seek Fast Track designation for other product candidates. Even if received, Fast Track designation may not actually lead to a faster review or approval process and does not increase the likelihood that our product candidates will receive marketing approval.

We have received Fast Track designation for ITIL-168 for the treatment of metastatic melanoma, and we may seek Fast Track designation for our other product candidates. If a drug or biologic is intended for the treatment of a serious or life-threatening condition and the product demonstrates the potential to address unmet medical needs for this condition, the sponsor may apply for FDA Fast Track designation for a particular indication. There is no assurance that the FDA will grant this status to any of our other product candidates. If granted, Fast Track designation makes a product eligible for more frequent interactions with FDA to discuss the development plan and clinical trial design, as well as rolling review of the application, which means that the company can submit completed sections of its marketing application for review prior to completion of the entire submission. Marketing applications of product candidates with Fast Track designation may qualify for priority review under the policies and procedures offered by the FDA, but the Fast Track designation does not assure any such qualification or ultimate marketing approval by the FDA. The FDA has broad discretion whether or not to grant Fast Track designation, so even if we believe a particular product candidate is eligible for this designation, there can be no assurance that the FDA would decide to grant it. Even if we do receive Fast Track designation, we may not experience a faster development process, review or approval compared to conventional FDA procedures, and receiving a Fast Track designation does not provide any assurance of ultimate FDA approval. In addition, the FDA may withdraw Fast Track designation at any time if it believes that the designation is no longer supported by data from our clinical development program.

The regulatory approval processes of the FDA, EMA and comparable foreign authorities are lengthy, time consuming and inherently unpredictable. If we are not able to obtain required regulatory approval for our product candidates, our business will be substantially harmed.

The time required to obtain approval or other marketing authorizations by the FDA, EMA and comparable foreign authorities is unpredictable, and it 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, and 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. We have not obtained regulatory approval for any product candidate, and it is possible that we may never obtain regulatory approval for any product candidates we may seek to develop in the future. Neither we nor any current or future collaborator is permitted to market any drug product candidates in the United States until we receive regulatory approval of a BLA from the FDA, and we cannot market it in the European Union until we receive approval for a MAA from the EMA, or other required regulatory approval in other countries. To date, we have had only limited discussions with the FDA, EMA and the Medicines and Healthcare products Regulatory Agency regarding clinical development programs or regulatory approval for any product candidate within the United States, European Union and United Kingdom, respectively. In addition, we have no discussions with other comparable foreign authorities, regarding clinical development programs or regulatory approval for any product candidate outside of those jurisdictions.

Prior to obtaining approval to commercialize any drug 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,

EMA or other foreign regulatory agencies, that such product candidates are safe, pure and effective for their intended uses. 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 may also require us to conduct additional preclinical studies or clinical trials for our product candidates either prior to or after approval, or it may object to elements of our clinical development programs.

Our product candidates could fail to receive regulatory approval for many reasons, including the following:

- 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;
- the results of clinical trials may not meet the level of statistical significance required by the FDA or comparable foreign regulatory authorities for 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 fail to approve 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 authorities may significantly change in a manner rendering our clinical data insufficient for approval.

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

We have invested a significant portion of our time and financial resources in the development of our clinical and preclinical product candidates. Our business is dependent on our ability to successfully complete preclinical and clinical development of, obtain regulatory approval for, and, if approved, successfully commercialize ITIL-168, ITIL-306 and any future product candidates in a timely manner.

Even if we eventually complete clinical testing and receive approval of a BLA or foreign marketing application for ITIL-168, ITIL-306 or any future product candidates, the FDA, EMA or the applicable foreign regulatory agency may grant approval or other marketing authorization contingent on the performance of costly additional clinical trials, including post-marketing clinical trials. The FDA, EMA or the applicable foreign regulatory agency also may approve or authorize for marketing a product candidate for a more limited indication or patient population than we originally request, and the FDA, EMA or applicable foreign regulatory agency may not approve or authorize the labeling that we believe is necessary or desirable for the successful commercialization of a product candidate. Any delay in obtaining, or inability to obtain, applicable regulatory approval or other marketing authorization would delay or prevent commercialization of that product candidate and would materially adversely impact our business and prospects.

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

Success in preclinical studies or earlier clinical trials, including the compassionate use program, may not be indicative of results in future clinical trials. Our product candidates may not have favorable results in later clinical trials, if any, or receive regulatory approval.

Success in preclinical testing and early clinical trials, including the compassionate use program, does not ensure that later clinical trials will generate the same results or otherwise provide adequate data to demonstrate the efficacy and safety of a product candidate. Preclinical tests and Phase 1 and Phase 2 clinical trials are primarily designed to test safety, to study pharmacokinetics and pharmacodynamics and to understand the side effects of product candidates at various doses and schedules. Success in preclinical or animal studies and early clinical trials does not ensure that later large-scale efficacy trials will be successful nor does it predict final results. For example, we may be unable to identify suitable animal disease models for our product candidates, which could delay or frustrate our ability to proceed into clinical trials or obtain marketing approval. Our product candidates may fail to show the desired safety and efficacy in clinical development despite having progressed through preclinical studies and initial clinical trials.

Many companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in late-stage clinical trials even after achieving promising results in preclinical testing and earlier-stage clinical trials. Data obtained from preclinical and clinical activities are subject to varying interpretations, which may delay, limit or prevent regulatory approval. In addition, we may experience regulatory delays or rejections as a result of many factors, including changes in regulatory policy during the period of our product candidate development. Any such delays could negatively impact our business, financial condition, results of operations and prospects.

Interim, "top-line" and preliminary results from our clinical trials that we announce or publish from time to time may change as more data become available and are subject to audit and verification procedures that could result in material changes in the final data.

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

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 development program, the approvability or commercialization of the particular product candidate or product and our company in general. In addition, the information we choose to publicly disclose regarding a particular study or clinical trial is based on what is typically extensive information, and you or others may not agree with what we determine is the material or otherwise appropriate information to include in our disclosure. Any information we determine not to disclose may ultimately be deemed meaningful by you or others with respect to future decisions, conclusions, views, activities or otherwise regarding a particular product candidate or our business. 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, product candidates may be harmed, which could significantly harm our business prospects.

Our preclinical studies and clinical trials may fail to demonstrate substantial evidence of the safety and efficacy of our product candidates, or serious adverse or unacceptable side effects may be identified during the development of our product candidates, which could prevent, delay or limit the scope of regulatory approval of our product candidates, limit their commercialization, increase our costs or necessitate the abandonment or limitation of the development of some of our product candidates.

To obtain the requisite regulatory approvals for the commercial sale of our product candidates, we must demonstrate through lengthy, complex and expensive preclinical testing and clinical trials that our product candidates are safe, pure and potent for use in each target indication. These trials are expensive and time consuming, and their outcomes are inherently uncertain. Failures can occur at any time during the development process. Preclinical studies and clinical trials often fail to demonstrate safety or efficacy of the product candidate studied for the target indication, and most product candidates that begin clinical trials are never approved.

We may fail to demonstrate with substantial evidence from adequate and well-controlled trials, and to the satisfaction of the FDA or comparable foreign regulatory authorities, that our product candidates are safe and potent for their intended uses.

Possible adverse side effects that could occur with treatment with cell therapy products include thrombocytopenia, chills, anemia, pyrexia, febrile neutropenia, diarrhea, neutropenia, vomiting, hypotension, dyspnea, cytokine release syndrome and neurotoxicity. If our product candidates are associated with undesirable effects in preclinical studies or clinical trials or have characteristics that are unexpected, we may decide or be required to perform additional preclinical studies or to halt or delay further clinical development of our product candidates or to limit their development to more narrow uses or subpopulations in which the undesirable side effects or other characteristics are less prevalent, less severe, or more acceptable from a risk-benefit perspective, which may limit the commercial expectations for the product candidate, if approved. These side effects may not be appropriately recognized or managed by the treating medical staff, as toxicities resulting from personalized cell therapy, as with our TIL product candidates, are not normally encountered in the general patient population and by medical personnel. Further, patients in the United Kingdom have been treated under a compassionate use program with a TIL product that was manufactured using a prior version of the ITIL-168 manufacturing process. To the extent the experiences of patients being treated in this program are inconsistent with the results of our ongoing company-sponsored trials of ITIL-168, it may negatively affect perceptions of ITIL-168 or our business. In addition, the FDA, EMA or other foreign regulatory authorities may require us to obtain and submit additional nonclinical data supporting the comparability of our ITIL-168 product candidate with the TIL product evaluated in the compassionate use study in the United Kingdom, or may not permit us to rely on the data from the compassionate use program to support the development of ITIL-168 at all, which could delay clinical development or marketing approval of ITIL-168.

If any such adverse events occur, our clinical trials could be suspended or terminated. If we cannot demonstrate that any adverse events were not caused by the drug, the FDA, EMA or foreign regulatory authorities could order us to cease further development of, or deny approval of, our product candidates for any or all targeted indications. Even if we are able to demonstrate that all future serious adverse events are not product-related, such occurrences could affect patient recruitment or the ability of enrolled patients to complete the trial. Moreover, if we elect, or are required, to not initiate, delay, suspend or terminate any future clinical trial of any of our product candidates, the commercial prospects of such product candidates may be harmed and our ability to generate product revenues from any of these product candidates may be delayed or eliminated. Any of these occurrences may harm our ability to develop other product candidates, and may harm our business, financial condition and prospects significantly.

If our product candidates are associated with side effects in clinical trials or have characteristics that are unexpected, we may need to abandon their development or limit development to more narrow uses in which the side effects or other characteristics are less prevalent, less severe or more acceptable from a risk-benefit perspective. The FDA or an IRB may also require that we suspend, discontinue, or limit our clinical trials based on safety information, or that we conduct additional animal or human studies regarding the safety and efficacy of our product candidates which we have not planned or anticipated. Such findings could further result in regulatory authorities failing to provide marketing authorization for our product candidates or limiting the scope of the approved indication, if approved. Many product candidates that initially showed promise in early stage testing have later been found to cause side effects that prevented further development of the product candidate.

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

- regulatory authorities may suspend, withdraw or limit approvals of such product, or seek an injunction against its manufacture or distribution;
- regulatory authorities may require additional warnings on the label;
- we may be required to create a medication guide outlining the risks of such side effects for distribution to patients or other requirements subject to a REMS;
- we may be required to change the way a product is administered or conduct additional trials;
- we could be sued and held liable for harm caused to patients;
- we may decide to remove the product from the market;
- we may not be able to achieve or maintain third-party payor coverage and adequate reimbursement;
- we may be subject to fines, injunctions or the imposition of civil or criminal penalties; and
- our reputation and physician or patient acceptance of our products may suffer.

There can be no assurance that we will resolve any issues related to any product-related adverse events to the satisfaction of the FDA or foreign regulatory agency in a timely manner or at all. Moreover, any of these events could prevent us from achieving or maintaining market acceptance of the particular product candidate, if approved, and could significantly harm our business, results of operations and prospects.

Negative public opinion of TIL therapies and increased regulatory scrutiny of cell therapy using TILs may adversely impact the development or commercial success of our current and future product candidates.

The clinical and commercial success of our TIL therapies will depend in part on public acceptance of the use of cell therapy using TILs. Any adverse public attitudes about the use of TIL therapies may adversely impact our ability to enroll clinical trials. Moreover, our success will depend upon physicians prescribing, and their patients being willing to receive, treatments that involve the use of product candidates we may develop in lieu of, or in addition to, existing treatments with which they are already familiar and for which greater clinical data may be available.

More restrictive government regulations or negative public opinion would have a negative effect on our business or financial condition and may delay or impair the development and commercialization of our product candidates or demand for any products once approved. Adverse events in our or others' clinical trials, even if not ultimately attributable to our product candidates, and the resulting publicity could result in increased governmental regulation, unfavorable public perception, potential regulatory delays in the testing or approval of our product candidates, stricter labeling requirements for those product candidates that are approved and a decrease in demand for any such product candidates, all of which would have a negative impact on our business and ***operations.***

As an organization, we are early in the process of conducting our first clinical trial, have no prior experience in conducting clinical trials, and may be unable to do so for any product candidates we may develop, including ITIL-168.

We are early in our development efforts for our product candidates, and will need to successfully complete our ongoing and planned clinical trials, including pivotal clinical trials, in order to obtain FDA approval to market any of our product candidates. Carrying out clinical trials and the submission of a successful BLA is a complicated process. As an organization, we are early in the process of conducting our first multi-center clinical trial with centralized manufacturing, have no prior experience in conducting any clinical trials, have limited experience in preparing regulatory submissions and have not previously submitted a BLA for any product candidate. We have only previously treated patients with our TIL product in a compassionate use program. In addition, we have had limited interactions with the FDA and cannot be certain how many additional clinical trials of our product candidates will be required or how such trials should be designed. Consequently, we may be unable to successfully and efficiently execute and complete necessary clinical trials in a way that leads to BLA submission and approval of any product candidate. We may require more time and incur greater costs than our competitors and may not succeed in obtaining

regulatory approvals of product candidates that we develop. Failure to commence or complete, or delays in, our planned clinical trials, could prevent us from or delay us in commercializing our product candidates.

We may experience delays or difficulties in the enrollment and/or retention of patients in clinical trials, which could delay or prevent our receipt of necessary regulatory approvals.

Successful and timely completion of clinical trials will require that we enroll a sufficient number of patients. Patient enrollment, a significant factor in the timing of clinical trials, is affected by many factors, including the size and nature of the patient population and competition for patients eligible for our clinical trials with competitors which may have ongoing clinical trials for product candidates that are under development to treat the same indications as one or more of our product candidates, or approved products for the conditions for which we are developing our product candidates.

Trials may be subject to delays as a result of patient enrollment taking longer than anticipated or patient withdrawal. We may not be able to initiate or continue clinical trials for our product candidates if we are unable to locate and enroll a sufficient number of eligible patients to participate in these trials as required by the FDA or foreign regulatory authorities. We cannot predict how successful we will be at enrolling subjects in future clinical trials. Subject enrollment is affected by other factors including:

- the severity and difficulty of diagnosing the disease under investigation;
- the eligibility and exclusion criteria for the trial in question;
- the size of the patient population and process for identifying patients;
- our ability to recruit clinical trial investigators with the appropriate competencies and experience;
- the design of the trial protocol;
- the perceived risks and benefits of the product candidate in the trial, including relating to cell therapy approaches;
- the availability of competing commercially available therapies and other competing therapeutic candidates' clinical trials for the disease or condition under investigation;
- the willingness of patients to be enrolled in our clinical trials;
- the efforts to facilitate timely enrollment in clinical trials;
- potential disruptions caused by the COVID-19 pandemic, including difficulties in initiating clinical sites, enrolling and retaining participants, diversion of healthcare resources away from clinical trials, travel or quarantine policies that may be implemented, and other factors;
- the patient referral practices of physicians;
- the ability to monitor patients adequately during and after treatment; and
- the proximity and availability of clinical trial sites for prospective patients.

Our inability to enroll a sufficient number of patients for clinical trials would result in significant delays and could require us to abandon one or more clinical trials altogether. Enrollment delays in these clinical trials may result in increased development costs for our product candidates, which would cause the value of our company to decline and limit our ability to obtain additional financing. Furthermore, we expect to rely on CROs and clinical trial sites to ensure the proper and timely conduct of our clinical trials and we will have limited influence over their performance.

Furthermore, even if we are able to enroll a sufficient number of patients for our clinical trials, we may have difficulty maintaining enrollment of such patients in our clinical trials.

We have received orphan designation for ITIL-168 for the treatment of malignant melanoma stages IIB to IV and may seek orphan drug designation for future product candidates. We may be unsuccessful, or may

be unable to maintain the benefits associated with orphan drug designation, including the potential for market exclusivity, for product candidates for which we obtain orphan drug designation.

We have obtained orphan designation for ITIL-168 for the treatment of malignant melanoma stages of IIB to IV and may seek orphan drug designation for some or all of our product candidates in specific orphan indications in which there is a medically plausible basis for the use of these product candidates. Under the Orphan Drug Act, the FDA may grant orphan drug designation to a drug or biologic intended to treat a rare disease or condition, defined as a patient population of fewer than 200,000 individuals in the United States, or a patient population of 200,000 or more in the United States where there is no reasonable expectation that the cost of developing and making available the drug or biologic will be recovered from sales in the United States. Orphan drug designation must be requested before submitting a BLA. Although we may seek orphan drug designation for some or all of our product candidates, we may never receive such designations.

In the United States, orphan drug designation entitles a party to financial incentives such as tax advantages and user fee waivers. Opportunities for grant funding toward clinical trial costs may also be available for clinical trials of drugs or biologics for rare diseases, regardless of whether the drugs or biologics are designated for the orphan use.

In addition, if a drug or biologic with an orphan drug designation subsequently receives the first marketing approval for a particular active ingredient or principal molecular structural features for the indication for which it has such designation, the product is entitled to a seven year period of marketing exclusivity, which precludes the FDA from approving another marketing application for the same drug and indication for that time period, except in limited circumstances such as a showing of clinical superiority to the product with orphan drug exclusivity or if the FDA finds that the holder of the orphan drug exclusivity has not shown that it can ensure the availability of sufficient quantities of the orphan product to meet the needs of patients with the disease or condition for which the drug was designated. Even if we obtain orphan drug designation for a product candidate, we may not be the first to obtain marketing approval for any particular orphan indication due to the uncertainties associated with developing biological products. If we seek orphan drug designation, we may be unsuccessful in obtaining such orphan drug designation for our product candidates. Even if we obtain orphan drug exclusivity for any of our product candidates, we may be unable to maintain the benefits associated with orphan drug designation, or such orphan drug exclusivity may not effectively protect those product candidates from competition because different drugs can be approved for the same condition, and orphan drug exclusivity does not prevent the FDA from approving the same or a different drug in another indication. Even after an orphan drug is granted orphan exclusivity and approved, the FDA can subsequently approve a later application for the same drug for the same condition before the expiration of the seven-year exclusivity period if the FDA concludes that the later drug is clinically superior in that it is shown to be safer in a substantial portion of the target populations, more effective or makes a major contribution to patient care. In addition, a designated orphan drug may not receive orphan drug exclusivity if it is approved for a use that is broader than the indication for which it received orphan designation. Moreover, orphan-drug-exclusive marketing rights in the United States may be lost if the FDA later determines that the request for designation was materially defective or that we are unable to manufacture sufficient quantities of the product to meet the needs of patients with the rare disease or condition. 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.

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

We may, in the future, apply for breakthrough therapy designation, or the equivalent thereof in foreign jurisdictions (where available), for our product candidates. A breakthrough therapy is defined as a product candidate that is intended, alone or in combination with one or more other drugs, to treat a serious or life-threatening disease or condition, and preliminary clinical evidence indicates that the product candidate may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. For product candidates that have been designated as breakthrough therapies, interaction and communication between the FDA and the sponsor of the trial can help to identify the most efficient path for clinical development while minimizing the number of patients placed in ineffective control

regimens. Product candidates designated as breakthrough therapies by the FDA are also eligible for priority review if supported by clinical data at the time of the submission of the BLA.

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

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

Because we have limited financial and management resources, we must focus on development programs and product candidates that we identify for specific indications. As such, we are currently primarily focused on the development of ITIL-168 for the treatment of PD-1-inhibitor-relapsed or refractory advanced melanoma. As a result, we may forego or delay pursuit of opportunities with other product candidates or for other indications for these product candidates that later prove to have greater commercial potential. Our resource allocation decisions may cause us to fail to capitalize on viable commercial products or profitable market opportunities. Our spending on current and future development programs and product candidates for specific indications may not yield any commercially viable products. If we do not accurately evaluate the commercial potential or target market for a particular product candidate, we may relinquish valuable rights to that product candidate through collaboration, licensing or other royalty arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to such product candidate.

We plan to conduct and may in the future conduct additional clinical trials for our product candidates outside the United States, and the FDA and similar foreign regulatory authorities may not accept data from such trials conducted in locations outside of their jurisdiction.

We may in the future choose to conduct clinical trials outside the United States, including in Australia, Canada, Europe or other foreign jurisdictions. The acceptance of trial data from clinical trials conducted outside the United States by the FDA may be subject to certain conditions or may not be accepted at all. In cases where data from clinical trials conducted outside the United States are intended to serve as the sole basis for marketing approval in the United States, the FDA will generally not approve the application on the basis of foreign data alone unless (i) the data are applicable to the United States population and United States medical practice; (ii) the trials were performed by clinical investigators of recognized competence and (iii) the data may be considered valid without the need for an on-site inspection by the FDA or, if the FDA considers such an inspection to be necessary, the FDA is able to validate the data through an on-site inspection or other appropriate means. Additionally, the FDA's clinical trial requirements, including sufficient size of patient populations and statistical powering, must be met. Many foreign regulatory bodies have similar approval requirements. In addition, such foreign trials would be subject to the applicable local laws of the foreign jurisdictions where the trials are conducted. There can be no assurance that the FDA or any similar foreign regulatory authority will accept data from trials conducted outside of the United States or the applicable jurisdiction. If the FDA or any similar foreign regulatory authority does not accept such data, it would result in the need for additional trials, which would be costly and time-consuming and delay aspects of our business plan, and which may result in our product candidates not receiving approval or clearance for commercialization in the applicable jurisdiction.

We may not be successful in our efforts to build a pipeline of additional product candidates.

We may not be able to continue to identify and develop new product candidates in addition to our current pipeline. Even if we are successful in continuing to build our pipeline, the potential product candidates that we identify may not be suitable for clinical development. For example, product candidates may be shown to have

harmful side effects or other characteristics that indicate that they are unlikely to be successfully developed, much less receive marketing approval and achieve market acceptance. If we do not successfully develop and commercialize product candidates based upon our approach, we will not be able to obtain product revenue in future periods, which likely would result in significant harm to our financial position and adversely affect our stock price.

If we do not achieve our projected development goals in the time frames we announce and expect, the commercialization of our products may be delayed.

From time to time, we may estimate the timing of the accomplishment of various scientific, clinical, regulatory, manufacturing and other product development goals, which we sometimes refer to as milestones. These milestones may include the commencement or completion of preclinical studies and clinical trials and the submission of regulatory filings, including IND submissions. From time to time, we may publicly announce the expected timing of some of these milestones. All of these milestones are, and will be, based on a variety of assumptions. The actual timing of these milestones can vary significantly compared to our estimates, in some cases for reasons beyond our control. We may experience numerous unforeseen events during, or as a result of, any future clinical trials that we conduct that could delay or prevent our ability to receive marketing approval or commercialize our product candidates.

Our business and operations may be adversely affected by the evolving and ongoing COVID-19 global pandemic.

Our business and operations may be adversely affected by the effects of the recent and evolving COVID-19 virus, which was declared a global pandemic by the World Health Organization. The COVID-19 pandemic has resulted in travel and other restrictions in order to reduce the spread of the disease, including public health directives and orders in the United States and the European Union that, among other things and for various periods of time, directed individuals to shelter at their places of residence, directed businesses and governmental agencies to cease non-essential operations at physical locations, prohibited certain non-essential gatherings and events and ordered cessation of non-essential travel. Future remote work policies and similar government orders or other restrictions on the conduct of business operations related to the COVID-19 pandemic may negatively impact productivity and may disrupt our ongoing research and development activities and our clinical programs and timelines, the magnitude of which will depend, in part, on the length and severity of the restrictions and other limitations on our ability to conduct our business in the ordinary course. Further, such orders also may impact the availability or cost of materials, which would disrupt our supply chain and manufacturing efforts and could affect our ability to conduct ongoing and planned clinical trials and preparatory activities.

Although our planned clinical trials have not been impacted by the COVID-19 pandemic to date, we may experience related disruptions in the future that could severely impact our clinical trials, including:

- delays, difficulties or a suspension in clinical site initiation, including difficulties in recruiting clinical site investigators and clinical site staff;
- interruptions in our ability to manufacture and deliver drug supply for trials;
- 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;
- changes in local regulations as part of a response to the COVID-19 outbreak that may require us to change the ways in which our clinical trials are conducted, which may result in unexpected costs, or to discontinue the clinical trials altogether;
- interruption of key clinical trial activities, such as clinical trial site monitoring, and the ability or willingness of subjects to travel to trial sites due to limitations on travel imposed or recommended by federal or state governments, employers and others;

- limitations in 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;
- delays in necessary interactions with local regulators, ethics committees and other important agencies and contractors due to limitations in employee resources or forced furlough of government employees; and
- refusal of the FDA to accept data from clinical trials in these affected geographies.

The spread of COVID-19, including the emergence and spread of the Delta and Omicron variants, which has caused a broad impact globally, may materially affect us economically. While the potential economic impact brought by, and the duration of, the COVID-19 pandemic may be difficult to assess or predict, a widespread pandemic could result in significant disruption of global financial markets, reducing our ability to access capital, which could in the future negatively affect our liquidity. In addition, a recession or market correction resulting from the spread of COVID-19 could materially affect our business and the value of our common stock.

The global COVID-19 pandemic continues to rapidly evolve. The extent to which the COVID-19 pandemic impacts our business and operations, including our clinical development and regulatory efforts, will depend on future developments that are highly uncertain and cannot be predicted with confidence at the time of this Annual Report on Form 10-K, such as the ultimate geographic spread of the disease, the duration of the outbreak, the duration and effect of business disruptions and the short-term effects and ultimate effectiveness of the travel restrictions, quarantines, social distancing requirements and business closures in the United States and other countries to contain and treat the disease. Accordingly, we do not yet know the full extent of potential delays or impacts on our business, our clinical and regulatory activities, healthcare systems or the global economy as a whole. However, these impacts could adversely affect our business, financial condition, results of operations and growth prospects.

In addition, to the extent the ongoing COVID-19 pandemic adversely affects our business and results of operations, it may also have the effect of heightening many of the other risks and uncertainties described in this “Risk Factors” section.

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

Any revenue we are able to generate in the future from product sales will be dependent, in part, upon the size of the market in the United States and any other jurisdiction for which we gain regulatory approval and have commercial rights. If the markets or patient subsets that we are targeting are not as significant as we estimate, we may not generate significant revenues from sales of such products, even if approved.

Cancer therapies are sometimes characterized as first-line, second-line or third-line, and the FDA often approves new therapies initially only for third-line use. When cancer is detected early enough, first-line therapy, usually chemotherapy, immunotherapy, hormone therapy, surgery, radiation therapy or a combination of these, is sometimes adequate to cure the cancer or prolong life without a cure. Second- and third-line therapies are administered to patients when prior therapy is not effective. We may initially seek approval for ITIL-168, ITIL-306 and any other product candidates we develop as a therapy for patients who have received one or more prior treatments. If we do so, for those products that prove to be sufficiently beneficial, if any, we would expect to seek approval potentially as a first-line therapy, but there is no guarantee that any product candidate we develop, even if approved, would be approved for first-line therapy, and, prior to any such approvals, we may have to conduct additional clinical trials.

The number of patients who have the types of cancer we are targeting may turn out to be lower than expected. Additionally, the potentially addressable patient population for our current or future product candidates may be limited, if and when approved. Further, even if any of our product candidates are approved by the FDA or comparable foreign regulators, their approved indications may be limited to a subset of the indications that we

targeted. Even if we obtain significant market share for any product candidate, if and when approved, if the potential target populations are small, we may never achieve profitability without obtaining marketing approval for additional indications, including to be used as first- or second-line therapy.

We may develop ITIL-168, ITIL-306 and future product candidates for use in combination with other therapies or third-party product candidates, which exposes us to additional regulatory risks.

We may develop ITIL-168, ITIL-306 and future product candidates for use in combination with one or more currently approved cancer therapies. Even if any product candidate we develop were to receive marketing approval or be commercialized for use in combination with other existing therapies, we would continue to be subject to the risk that the FDA, EMA or comparable foreign regulatory authorities could revoke approval of the therapy used in combination with our product candidate or that safety, efficacy, manufacturing or supply issues could arise with these existing therapies. This could result in our own products being removed from the market or being less successful commercially. Combination therapies are commonly used for the treatment of cancer, and we would be subject to similar risks if we develop any of our product candidates for use in combination with other drugs or for indications other than cancer.

We may also evaluate ITIL-168, ITIL-306 or any future product candidate in combination with one or more other third party product candidates that have not yet been approved for marketing by the FDA, EMA or comparable foreign regulatory authorities. If so, we will not be able to market and sell ITIL-168, ITIL-306 or any product candidate we develop in combination with any such unapproved cancer therapies that do not ultimately obtain marketing approval.

If the FDA or comparable foreign regulatory authorities do not approve these other biological products or revoke their approval of, or if safety, efficacy, manufacturing or supply issues arise with, the biologics we choose to evaluate in combination with ITIL-168, ITIL-306 or any product candidate we develop, we may be unable to obtain approval of or market any such product candidate.

The United Kingdom's withdrawal from the European Union may have a negative effect on global economic conditions, financial markets and our business.

Following the result of a referendum in 2016, the United Kingdom left the European Union on January 31, 2020, commonly referred to as Brexit. Pursuant to the formal withdrawal arrangements agreed to by the United Kingdom and the European Union, as of January 1, 2021, the United Kingdom is no longer subject to the transition period, or the Transition Period, during which European Union rules continued to apply. Negotiations between the United Kingdom and the European Union are expected to continue in relation to the customs and trading relationship between the United Kingdom and the European Union following the expiry of the Transition Period.

We have significant operations in the United Kingdom. Further, since a significant proportion of the regulatory framework in the United Kingdom is applicable to our business and our product candidates is derived from European Union directives and regulations, Brexit, following the Transition Period, could materially impact the regulatory regime with respect to the development, manufacture, importation, approval and commercialization of our product candidates in the United Kingdom or the European Union. For example, as a result of the uncertainty surrounding Brexit, the EMA relocated to Amsterdam from London. Following the Transition Period, the United Kingdom will no longer be covered by the centralized procedures for obtaining European Union-wide marketing authorizations from the EMA and, unless a specific agreement is entered into, a separate process for authorization of drug products will be required in the United Kingdom, the potential process for which is currently unclear. 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 United Kingdom or the European Union and limit our ability to generate revenue and achieve and sustain profitability. In addition, we may be required to pay taxes or duties or be subjected to other hurdles in connection with the importation of our product candidates into the European Union, or we may incur expenses in establishing a manufacturing facility in the European Union in order to circumvent such hurdles. If any of these outcomes occur, we may be forced to restrict or delay efforts to seek regulatory approval in the United Kingdom or the European Union for our product candidates, or incur significant additional expenses to operate our business, which could significantly and materially harm or delay our ability to

generate revenues or achieve profitability of our business. Any further changes in international trade, tariff and import/export regulations as a result of Brexit or otherwise may impose unexpected duty costs or other non-tariff barriers on us. These developments, or the perception that any of them could occur, may significantly reduce global trade and, in particular, trade between the impacted nations and the United Kingdom. It is also possible that Brexit may negatively affect our ability to attract and retain employees, particularly those from the European Union.

Risks Related to the Manufacturing of our Product Candidates

Cell therapies are complex and difficult to manufacture. We could experience manufacturing problems that result in delays in the development or commercialization of our product candidates or otherwise harm our business.

The manufacture of cell therapy products is technically complex and necessitates substantial expertise and capital investment. Production difficulties caused by unforeseen events may delay the availability of material for our clinical studies.

The manufacturers of pharmaceutical products must comply with strictly enforced cGMP requirements, state and federal regulations, as well as foreign requirements when applicable. Any failure of us or our contract manufacturing organizations to adhere to or document compliance to such regulatory requirements could lead to a delay or interruption in the availability of our program materials for clinical trials or enforcement action from the FDA, EMA or foreign regulatory authorities. If we or our manufacturers were to fail to comply with the FDA, EMA or other regulatory authority, it could result in sanctions being imposed on us, including clinical holds, fines, injunctions, civil penalties, delays, suspension or withdrawal of approvals, license revocation, seizures or recalls of product candidates or products, operating restrictions and criminal prosecutions, any of which could significantly and adversely affect supplies of our product candidates. Our potential future dependence upon others for the manufacture of our product candidates may also adversely affect our future profit margins and our ability to commercialize any product candidates that receive regulatory approval on a timely and competitive basis.

Biological products are inherently difficult to manufacture. Our program materials are manufactured using technically complex processes requiring specialized equipment and facilities, highly specific raw materials, cells, and reagents, and other production constraints. Our production process requires a number of highly specific raw materials, cells and reagents with limited suppliers. Even though we aim to have backup supplies of raw materials, cells and reagents whenever possible, we cannot be certain they will be sufficient if our primary sources are unavailable. A shortage of a critical raw material, cell line, or reagent, or a technical issue during manufacturing may lead to delays in clinical development or commercialization plans. Any changes in the manufacturing of components of the raw materials we use could result in unanticipated or unfavorable effects in our manufacturing processes, resulting in delays.

Delays or failures in the manufacture of cell therapies (whether by us, any collaborator or our third party contract manufacturers) can result in a patient being unable to receive their cell therapy or a requirement to re-manufacture which itself then causes delays in manufacture for other patients. Any delay or failure or inability to manufacture on a timely basis can adversely affect a patient's outcomes and delay the timelines for our clinical trials. Such delays or failure or inability to manufacture can result from:

- a failure in the manufacturing process itself, for example by an error in manufacturing process (whether by us or our third party CMO), equipment or reagent failure, failure in any step of the manufacturing process, failure to maintain a GMP environment or failure in quality systems applicable to manufacture, sterility failures, contamination during process;
- product loss or failure due to logistical issues associated with the collection of a patient's tumor or other samples, shipping that material to analytical laboratories, and shipping the final product back to the location using cold chain distribution where it will be administered to the patient, manufacturing issues associated with the differences in patient starting materials, inconsistency in cell growth and variability in product characteristics;

- a lack of reliability or reproducibility in the manufacturing process itself leading to variability in end manufacture of cell therapy, which may lead to regulatory authorities placing a hold on a clinical trial or requesting further information on the process which could in turn result in delays to the clinical trials;
- variations in patient starting material or apheresis product resulting in less product than expected or product that is not viable, or that cannot be used to successfully manufacture a cell therapy;
- product loss or failure due to logistical issues including issues associated with the differences between patients' white blood cells or characteristics, interruptions to process, contamination, failure to supply patient apheresis material within required timescales (for example, as a result of an import or export hold-up) or supplier error;
- inability to obtain viral vector manufacturing slots from CMOs or to have enough manufacturing slots to manufacture cell therapies for patients as and when those patients require manufacture;
- inability to procure starting materials or to manufacture starting materials;
- loss of or close-down of any manufacturing facility used in the manufacture of our cell therapies, or the inability to find alternative manufacturing capability in a timely fashion;
- loss or contamination of patient starting material, requiring the starting material to be obtained again from the patient or the manufacturing process to be re-started; and
- a requirement to modify or make changes to any manufacturing process, which may also require comparability testing that delays our ability to make the required modifications or perform any required comparability testing in a timely fashion, require further regulatory approval or require successful tech transfer to CMOs to continue manufacturing.

Our product candidates are biologics and the manufacture of our product candidates is complex and we may encounter difficulties in production, particularly with respect to process development or scaling-out of our manufacturing capabilities. If we encounter such difficulties, our ability to provide supply of our product candidates for clinical trials or any approved products could be delayed or stopped.

All entities involved in the preparation of therapeutics for clinical trials or commercial sale, including our existing contract manufacturers for components our product candidates, are subject to extensive regulation. Components of a finished therapeutic product approved for commercial sale or used in late-stage clinical trials in the European Union must be manufactured in accordance with cGMP. These regulations govern manufacturing processes and procedures (including record keeping) and the implementation and operation of quality systems to control and assure the quality of investigational products and products approved for sale. Poor control of production processes can lead to the introduction of adventitious agents or other contaminants, or to inadvertent changes in the properties or stability of our product candidates that may not be detectable in final product testing. We or our contract manufacturers must supply all necessary documentation in support of a BLA or MAA on a timely basis. Our facilities and quality systems and the facilities and quality systems of some or all of our third-party contractors must pass a pre-approval inspection for compliance with the applicable regulations as a condition of regulatory approval of our product candidates or any of our other potential products. In addition, the regulatory authorities may, at any time, audit or inspect a manufacturing facility involved with the preparation of our product candidates or our other potential products or the associated quality systems for compliance with the regulations applicable to the activities being conducted, and they could put a hold on one or more of our clinical trials if the facilities of our contract development and manufacturing organizations do not pass such audit or inspections. If these facilities do not pass a pre-approval plant inspection, FDA approval of the products will not be granted.

The regulatory authorities also may, at any time following approval of a product for sale, inspect or audit our manufacturing facilities or those of our third-party contractors. If any such inspection or audit identifies a failure to comply with applicable regulations or if a violation of our product specifications or applicable regulations occurs independent of such an inspection or audit, we or the relevant regulatory authority may require remedial measures that may be costly and/or time-consuming for us or a third party to implement and that may include the temporary or permanent suspension of a clinical trial or commercial sales or the temporary or permanent closure of a facility. Any

such remedial measures imposed upon us or third parties with whom we contract could harm our business. If we or any of our third-party manufacturers fail to maintain regulatory compliance, the FDA can impose regulatory sanctions including, among other things, refusal to approve a pending application for a new drug product or biologic product, or revocation of a pre-existing approval. As a result, our business, financial condition and results of operations may be harmed. Additionally, if supply from one approved manufacturer is interrupted, there could be a significant disruption in commercial supply. An alternative manufacturer would need to be qualified through a BLA and/or MAA supplement which could result in further delay. The regulatory agencies may also require additional studies if a new manufacturer is relied upon for commercial production. Switching manufacturers may involve substantial costs and is likely to result in a delay in our desired clinical and commercial timelines.

These factors could cause the delay of clinical trials, regulatory submissions, required approvals or commercialization of our product candidates, cause us to incur higher costs and prevent us from commercializing our products successfully, if approved. Furthermore, if our suppliers fail to meet contractual requirements, and we are unable to secure one or more replacement suppliers capable of production at a substantially equivalent cost, our clinical trials may be delayed or we could lose potential revenue.

Although we are in the process of transferring the current manufacturing process of ITIL-168 from our manufacturing facility in Manchester, United Kingdom and establishing our manufacturing facility in Tarzana, California, we may utilize third parties if needed to manufacture our product candidates. Therefore, we are subject to the risk that such third parties may not perform satisfactorily.

Although we expect that our manufacturing facility will be the primary source of clinical and commercial supply for ITIL-168 and future product candidates, if approved, we may continue to rely on outside vendors for at least a portion of the manufacturing process and intend to evaluate potential third-party manufacturing capabilities if necessary to meet further clinical and commercial demand. In the event that we engage third-party manufacturers and they do not successfully carry out their contractual duties, meet expected deadlines or manufacture our product candidates in accordance with regulatory requirements or if there are disagreements between us and any third-party manufacturer, we may be delayed in producing sufficient clinical and commercial supply of our product candidates. In such instances, we may need to locate an appropriate replacement third-party relationship, which may not be readily available or on acceptable terms, which would cause additional delay or increased expense and would thereby have a material adverse effect on our business, financial condition, results of operations and prospects.

Reliance on third-party providers may expose us to more risk than if we were to manufacture product candidates ourselves. The facilities used by our contract manufacturers to manufacture our product candidates must be approved by the FDA pursuant to inspections that will be conducted after we submit our BLA to the FDA. We do not control the manufacturing process of, and are completely dependent on, our contract manufacturing partners for compliance with the regulatory requirements, known as cGMPs for the manufacture of our product candidates. If our contract manufacturers cannot successfully manufacture material that conforms to our specifications and the strict regulatory requirements of the FDA or others, they will not be able to secure and/or maintain regulatory approval for their manufacturing facilities. In addition, we have no control over the ability of our contract manufacturers to maintain adequate quality control, quality assurance and qualified personnel. If the FDA or a comparable foreign regulatory authority does not approve these facilities for the manufacture of our product candidates or if it withdraws any such approval in the future, we may need to find alternative manufacturing facilities, which would significantly impact our ability to develop, obtain regulatory approval for or market our product candidates, if approved. 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 manufacturing of our product candidates or that obtained approvals could be revoked, which would adversely affect our business and reputation. Furthermore, third-party providers may breach existing agreements they have with us because of factors beyond our control. They may also terminate or refuse to renew their agreement because of their own financial difficulties or business priorities, at a time that is costly or otherwise inconvenient for us. If we were unable to find adequate replacement or another acceptable solution in time, our clinical trials could be delayed or our commercial activities could be harmed.

We have initiated a technology transfer of the current manufacturing process of ITIL-168 from our manufacturing facility in Manchester, United Kingdom to our new manufacturing facility in Tarzana, California, and we intend to utilize material manufactured in our new manufacturing facility in our future clinical trials of ITIL-168.

This technology transfer process is still underway, and to date, we have not successfully produced a batch of ITIL-168. We will need to perform analytical and other animal or cell-based tests to demonstrate that materials produced by our new manufacturing facility, or any other third-party manufacturer that we engage, is comparable in all respects, including potency, to the product produced by our Manchester manufacturing facility and utilized in prior clinical and preclinical studies of ITIL-168. There is no assurance that we, or any other future third-party manufacturer that we engage, will be successful in producing ITIL-168, that any such product will pass the required comparability testing, or that any materials produced by us or any other third-party manufacturer that we engage will have the same effect in patients that we have observed to date with respect to materials produced by our Manchester manufacturing facility. Once the technology transfer is complete, we believe that our manufacturing network will have sufficient capacity to meet demand for ITIL-168 for our future United States clinical trials. Although we have identified additional third-party cGMP-compliant manufacturers that we believe we will be able to contract with in order to provide additional sources of such materials, there is a risk that if supplies are interrupted or result in poor yield or quality, it would materially harm our business. In addition, we may change our manufacturing process for ITIL-168, which could cause delays in production as we and our third-party manufacturers seek to improve and streamline the process.

In addition, we do not currently have long-term supply or manufacturing arrangements in place for the production of ITIL-168. Although we intend to establish multiple sources for long-term supply, including our own commercial-scale cGMP-compliant manufacturing facility and one or more third-party manufacturers, if the cell therapy industry were to grow, we may encounter increasing competition for the raw materials and consumables necessary for the production of ITIL-168. Furthermore, demand for third-party cGMP manufacturing facilities may grow at a faster rate than existing manufacturing capacity, which could disrupt our ability to find and retain third-party manufacturers capable of producing sufficient quantities of ITIL-168 for future clinical trials or to meet initial commercial demand in the United States. In addition to our own manufacturing facilities, we currently rely, and expect to continue to rely, on additional third parties to manufacture ingredients of our product candidates and to perform quality testing. Even following our establishment of our own cGMP-compliant manufacturing capabilities, we intend to maintain third-party manufacturers for these ingredients, as well as to serve as additional sources of our product candidates, which will expose us to risks including:

- reduced control for certain aspects of manufacturing activities;
- termination or nonrenewal of manufacturing and service agreements with third parties in a manner or at a time that is costly or damaging to us; and
- disruptions to the operations of our third-party manufacturers and service providers caused by conditions unrelated to our business or operations, including the bankruptcy of the manufacturer or service provider.

Building our new manufacturing facility will require additional investment, will be time-consuming and may be subject to delays, including because of shortage of labor or compliance with regulatory requirements. In addition, building a manufacturing facility may cost more than we currently anticipate. Delays or problems in the build out of our manufacturing facility may adversely impact our ability to provide supply for the development and commercialization of ITIL-168, as well as our financial condition.

Any of these events could lead to clinical trial delays or failure to obtain regulatory approval, or impact our ability to successfully commercialize ITIL-168. Some of these events could be the basis for FDA action, including injunction, recall, seizure or total or partial suspension of product manufacture.

Our current operations are concentrated in two locations. We or the third parties upon whom we depend may be adversely affected by earthquakes, wildfires or other natural disasters, and our business continuity and disaster recovery plans may not adequately protect us from a serious disaster.

We are in the process of transitioning from our manufacturing facility in Manchester, United Kingdom to our new manufacturing facility in Tarzana, California. Any unplanned event, such as flood, fire, explosion, earthquake, extreme weather condition, medical epidemics or pandemics, power shortage, telecommunication failure or other natural or manmade accidents or incidents that result in us being unable to fully utilize our facilities may have a

material and adverse effect on our ability to operate our business, particularly on a daily basis, and have significant negative consequences on our financial and operating conditions. Loss of access to these facilities may result in increased costs, delays in the development of our product candidates or interruption of our business operations. Earthquakes, wildfires or other natural disasters could further disrupt our operations, and have a material and adverse effect on our business, financial condition, results of operations and prospects. If a natural disaster, power outage or other event prevented us from using all or a significant portion of our manufacturing facilities, or otherwise disrupted operations, it may be difficult or, in certain cases, impossible, for us to continue our business for a substantial period of time. The disaster recovery and business continuity plans we have in place may prove inadequate in the event of a serious disaster or similar event. We may incur substantial expenses as a result of the limited nature of our disaster recovery and business continuity plans, which could have a material adverse effect on our business. As part of our risk management policy, we maintain insurance coverage at levels that we believe are appropriate for our business. However, in the event of an accident or incident at these facilities, we cannot assure you that the amounts of insurance will be sufficient to satisfy any damages and losses. If our facilities are unable to operate because of an accident or incident or for any other reason, even for a short period of time, any or all of our research and development programs may be harmed. Any business interruption may have a material and adverse effect on our business, financial condition, results of operations and prospects.

We depend on third-party suppliers for materials that are necessary for the conduct of preclinical studies and manufacture of our product candidates for clinical trials, and the loss of these third-party suppliers or their inability to supply us with sufficient quantities of adequate materials, or to do so at acceptable quality levels and on a timely basis, could harm our business.

Manufacturing our product candidates requires many reagents, which are substances used in our manufacturing processes to bring about chemical or biological reactions, and other specialty materials and equipment, some of which are manufactured or supplied by small companies with limited resources and experience to support commercial biologics production. We currently depend on a limited number of vendors for certain materials and equipment used in the manufacture of our product candidates. For example, we currently use facilities and equipment at external contract manufacturing organizations, or CMOs, as well as supply sources internal to the collaboration for vector supply. Our use of CMOs increases the risk of delays in production or insufficient supplies as we transfer our manufacturing technology to these CMOs and as they gain experience with our supply requirements. Some of these suppliers may not have the capacity to support clinical trials and commercial products manufactured under cGMP by biopharmaceutical firms or may otherwise be ill-equipped to support our needs. We also do not have supply contracts with many of these suppliers and may not be able to obtain supply contracts with them on acceptable terms or at all. Accordingly, we may experience delays in receiving key materials and equipment to support clinical or commercial manufacturing.

For some of these reagents, equipment, and materials, we rely and may in the future rely on sole source vendors or a limited number of vendors. The supply of the reagents and other specialty materials and equipment that are necessary to produce our product candidates could be reduced or interrupted at any time. In such case, identifying and engaging an alternative supplier or manufacturer could result in delay, and we may not be able to find other acceptable suppliers or manufacturers on acceptable terms, or at all. Switching suppliers or manufacturers may involve substantial costs and is likely to result in a delay in our desired clinical and commercial timelines. If we change suppliers or manufacturers for commercial production, applicable regulatory agencies may require us to conduct additional studies or trials. If key suppliers or manufacturers are lost, or if the supply of the materials is diminished or discontinued, we may not be able to develop, manufacture and market our product candidates in a timely and competitive manner, or at all. An inability to continue to source product from any of these suppliers, which could be due to a number of issues, including regulatory actions or requirements affecting the supplier, adverse financial or other strategic developments experienced by a supplier, labor disputes or shortages, unexpected demands or quality issues, could adversely affect our ability to satisfy demand for our product candidates, which could adversely and materially affect our product sales and operating results or our ability to conduct clinical trials, either of which could significantly harm our business.

As we continue to develop and scale our manufacturing process, we expect that we will need to obtain rights to and supplies of certain materials and equipment to be used as part of that process. We may not be able to obtain

rights to such materials on commercially reasonable terms, or at all, and if we are unable to alter our process in a commercially viable manner to avoid the use of such materials or find a suitable substitute, it would have a material adverse effect on our business. Even if we are able to alter our process so as to use other materials or equipment, such a change may lead to a delay in our clinical development and/or commercialization plans. If such a change occurs for product candidate that is already in clinical testing, the change may require us to perform both ex vivo comparability studies and to collect additional data from patients prior to undertaking more advanced clinical trials. These factors could cause the delay of studies or trials, regulatory submissions, required approvals or commercialization of product candidates that we develop, cause us to incur higher costs and prevent us from commercializing our product candidates successfully.

Any contamination or interruption in our manufacturing process, shortages of raw materials or failure of our suppliers of reagents to deliver necessary components could result in delays in our clinical development or marketing schedules.

Given the nature of cell therapy manufacturing, there is a risk of contamination. Any contamination could adversely affect our ability to produce product candidates on schedule and could, therefore, harm our results of operations and cause reputational damage. Some of the raw materials required in our manufacturing process are derived from biologic sources. Such raw materials are difficult to procure and may be subject to contamination or recall. A material shortage, contamination, recall or restriction on the use of biologically derived substances in the manufacture of our product candidates could adversely impact or disrupt the commercial manufacturing or the production of clinical material, which could adversely affect our development timelines and our business, financial condition, results of operations and prospects.

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 product characteristics. Such changes carry the risk that they will not achieve our intended objectives. Any such 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, FDA notification or FDA approval. This could delay completion of clinical trials, require the conduct of bridging clinical trials or the repetition of one or more clinical trials, increase clinical trial costs, delay approval of our product candidates and jeopardize our ability to commence sales and generate revenue. In addition, we may be required to make significant changes to our upstream and downstream processes across our pipeline, which could delay the development of our future product candidates.

Risks Related to the Commercialization of our Product Candidates

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

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

- the efficacy, safety and potential advantages compared to alternative treatments;
- our ability to offer our products for sale at competitive prices;
- the convenience and ease of administration compared to alternative treatments;

- product labeling or product insert requirements of the FDA, EMA or other foreign regulatory authorities, including any limitations or warnings contained in a product's approved labeling, including any black box warning or REMS;
- the willingness of the target patient population to try new treatments and of physicians to prescribe these treatments;
- our ability to hire and retain a sales force in the United States;
- the strength of marketing and distribution support;
- the availability of third-party coverage and adequate reimbursement for ITIL-168, ITIL-306 and any other product candidates, once approved;
- the prevalence and severity of any side effects; and
- any restrictions on the use of our products together with other medications.

If we are unable to establish sales, marketing and distribution capabilities for ITIL-168, ITIL-306 or any other product candidate that may receive regulatory approval, we may not be successful in commercializing those product candidates if and when they are approved.

We do not have sales or marketing infrastructure. To achieve commercial success for ITIL-168, ITIL-306 or any other product candidate for which we may obtain marketing approval, we will need to establish a sales and marketing organization. In the future, we expect to build a focused sales and marketing infrastructure to market our product candidates in the United States, if they are approved. There are risks involved with establishing our own sales, marketing and distribution capabilities. For example, recruiting and training a sales force is expensive and time consuming and could delay any product launch. If the commercial launch of a product candidate for which we recruit a sales force and establish marketing capabilities is delayed or does not occur for any reason, we would have prematurely or unnecessarily incurred these commercialization expenses. This may be costly, and our investment would be lost if we cannot retain or reposition our sales and marketing personnel.

Factors that may inhibit our efforts to market our products 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 in order to educate physicians about our product candidates, once approved;
- the lack of complementary products to be offered by sales personnel, which may put us at a competitive disadvantage relative to companies with more extensive product lines; and
- unforeseen costs and expenses associated with creating an independent sales and marketing organization.

If we are unable to establish our own sales, marketing and distribution capabilities and are forced to enter into arrangements with, and rely on, third parties to perform these services, our revenue and our profitability, if any, are likely to be lower than if we had developed such capabilities ourselves. In addition, we may not be successful in entering into arrangements with third parties to sell, market and distribute our product candidates or may be unable to do so on terms that are favorable to us. We likely will have little control over such third parties, and any of them may fail to devote the necessary resources and attention to sell and market our products effectively. If we do not establish sales, marketing and distribution capabilities successfully, either on our own or in collaboration with third parties, we will not be successful in commercializing our product candidates.

The affected populations for our other product candidates may be smaller than we or third parties currently project, which may affect the addressable markets for our product candidates.

Our projections of the number of people who have the diseases we are seeking to treat, as well as the subset of people with these diseases who have the potential to benefit from treatment with our product candidates, are

estimates based on our knowledge and understanding of these diseases. These estimates may prove to be incorrect and new studies may further reduce the estimated incidence or prevalence of this disease. The number of patients in the United States, the European Union and elsewhere may turn out to be lower than expected, may not be otherwise amenable to treatment with our product candidates or patients may become increasingly difficult to identify and access, all of which would adversely affect our business, financial condition, results of operations and prospects. Further, even if we obtain approval for our product candidates, the FDA or other regulators may limit their approved indications to more narrow uses or subpopulations within the populations for which we are targeting development of our product candidates.

The total addressable market opportunity for our product candidates will ultimately depend upon a number of factors including the diagnosis and treatment criteria included in the final label, if approved for sale in specified indications, acceptance by the medical community, patient access and product pricing and reimbursement. Incidence and prevalence estimates are frequently based on information and assumptions that are not exact and may not be appropriate, and the methodology is forward-looking and speculative. The process we have used in developing an estimated incidence and prevalence range for the indications we are targeting has involved collating limited data from multiple sources. Accordingly, the incidence and prevalence estimates included in this Annual Report on Form 10-K or our other filings with the Securities and Exchange Commission, or the SEC, should be viewed with caution. Further, the data and statistical information used in this Annual Report on Form 10-K or our other filings with the SEC, including estimates derived from them, may differ from information and estimates made by our competitors or from current or future studies conducted by independent sources.

Off-label use or misuse of our products may harm our reputation in the marketplace, result in injuries that lead to costly product liability suits, and/or subject us to penalties if we fail to comply with regulatory requirements or experience unanticipated problems with any product.

If our product candidates are approved by the FDA, we may only promote or market our product candidates for their specifically approved indications. We will train our marketing and sales force against promoting our product candidates for uses outside of the approved indications for use, known as “off-label uses.” We cannot, however, prevent a physician from using our products off-label, when in the physician’s independent professional medical judgment he or she deems it appropriate. Furthermore, the use of our products for indications other than those approved by the FDA may not effectively treat such conditions. Any such off-label use of our product candidates could harm our reputation in the marketplace among physicians and patients. There may also be increased risk of injury to patients if physicians attempt to use our products for these uses for which they are not approved, which could lead to product liability suits that that might require significant financial and management resources and that could harm our reputation.

Advertising and promotion of any product candidate that obtains approval in the United States will be heavily scrutinized by the FDA, the U.S. Federal Trade Commission, the Department of Justice, or the DOJ, the Office of Inspector General of the U.S. Department of Health and Human Services, or HHS, state attorneys general, members of the U.S. Congress, and the public. Additionally, advertising and promotion of any product candidate that obtains approval outside of the United States will be heavily scrutinized by comparable foreign entities and stakeholders. Violations, including actual or alleged promotion of our products for unapproved or off-label uses, are subject to enforcement letters, inquiries, and investigations, and civil and criminal sanctions by the FDA, DOJ, or comparable foreign bodies. Any actual or alleged failure to comply with labeling and promotion requirements may result in fines, warning letters, mandates to corrective information to healthcare practitioners, injunctions, or civil or criminal penalties.

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

Drug development is highly competitive and subject to rapid and significant technological advancements. There are several large and small pharmaceutical companies focused on delivering therapeutics for the treatment of metastatic melanoma and other oncology indications we might target in the future. Further, it is likely that additional drugs will become available in the future for the treatment of our target indications.

We face competition from segments of the pharmaceutical, biotechnology and other related markets that pursue the development of TIL or other cell therapies for the treatment of solid tumors. Companies that are developing TIL therapies include Iovance Biotherapeutics Inc., Adaptimmune Therapeutics, Plc., Achilles Therapeutics, Ltd., Intima Bioscience, Inc., Nurix Therapeutics, Inc., KSQ Therapeutics, Inc., Obsidian Therapeutics, Inc., PACT Pharma, Inc., Lyell Immunopharma, Inc., and Neogene Therapeutics, B.V. In addition, we may face competition from companies focused on CAR-T and TCR-T cell therapies, such as Kite Pharma, Inc., a subsidiary of Gilead, Inc., Juno Therapeutics, Inc., a subsidiary of Bristol-Myers Squibb, Inc., TCR2 Therapeutics, Inc., Poseida Therapeutics, Inc. and Immatics N.V. There are also companies utilizing other cell-based approaches that may be competitive to our product candidates. For example, companies such as Celyad, S.A., Artiva Biotherapeutics, Inc., and Nkarta, Inc. are developing therapies that target and/or engineer natural killer, or NK, cells.

Many of our existing or potential competitors have substantially greater financial, technical and human resources than we do and significantly greater experience in the discovery and development of product candidates, as well as in obtaining regulatory approvals of those product candidates in the United States and in foreign countries. Our current and potential future competitors may also have significantly more experience commercializing drugs, particularly cell therapy and other biological products, that have been approved for marketing. Mergers and acquisitions in the pharmaceutical and biotechnology industries could result in even more resources being concentrated among a small number of our competitors.

We will face competition from other drugs or from other non-drug products currently approved or that will be approved in the future in the oncology field, including for the treatment of diseases and disorders in the therapeutic categories we intend to target. Therefore, our ability to compete successfully will depend largely on our ability to:

- develop and commercialize drugs that are superior to other products in the market;
- demonstrate through our clinical trials that our product candidates are differentiated from existing and future therapies;
- attract qualified scientific, product development and commercial personnel;
- obtain patent or other proprietary protection for our medicines;
- obtain required regulatory approvals;
- obtain coverage and adequate reimbursement from, and negotiate competitive pricing with, third-party payors; and
- successfully collaborate with pharmaceutical companies in the discovery, development and commercialization of new medicines.

The availability of our competitors' products could limit the demand, and the price we are able to charge, for any product candidate we develop. The inability to compete with existing or subsequently introduced drugs would have an adverse impact on our business, financial condition and prospects. In addition, the reimbursement structure of approved cell therapies by other companies could impact the anticipated reimbursement structure of our cell therapies, if approved, and our business, financial condition, results of operations and prospects.

Established pharmaceutical companies may invest heavily to accelerate discovery and development of novel compounds or to in-license novel compounds that could make our product candidates less competitive. In addition, any new product that competes with an approved product must demonstrate compelling advantages in efficacy, convenience, tolerability and safety in order to overcome price competition and to be commercially successful. Accordingly, our competitors may succeed in obtaining patent protection, discovering, developing, receiving regulatory and marketing approval for, or commercializing, drugs before we do, which would have an adverse impact on our business and results of operations.

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

If we are successful in achieving regulatory approval to commercialize any biologic product candidate that we develop, it may face competition from biosimilar products. In the United States, our product candidates are regulated by the FDA as biologic products subject to approval under the BLA pathway. The Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, or collectively, the ACA, includes a subtitle called the Biologics Price Competition and Innovation Act of 2009, or BPCIA, which created an abbreviated approval pathway for biological products that are biosimilar to or interchangeable with an FDA-licensed reference biological product. Under the BPCIA, an application for a biosimilar product may not be submitted to the FDA until four years following the date that the reference product was first licensed by the FDA. In addition, the approval of a biosimilar product may not be made effective by the FDA until 12 years from the date on which the reference product was first licensed by the FDA. During this 12-year period of exclusivity, another company may still market a competing version of the reference product if the FDA approves a full BLA for the competing product containing the sponsor's own preclinical data and data from adequate and well-controlled clinical trials to demonstrate the safety, purity and potency of their product. The law is complex and is still being interpreted and implemented by the FDA. As a result, its ultimate impact, implementation and meaning are subject to uncertainty. While it is uncertain when such processes intended to implement BPCIA may be fully adopted by the FDA, any such processes could have an adverse effect on the future commercial prospects for our biological products.

There is a risk that any of our product candidates approved as a biological product under a BLA would not qualify for the 12-year period of exclusivity or that this exclusivity could be shortened due to congressional action or otherwise, or that the FDA will not consider our product candidates to be reference products for competing products, potentially creating the opportunity for generic competition sooner than anticipated. Other aspects of the BPCIA, some of which may impact the BPCIA exclusivity provisions, have also been the subject of recent litigation. Moreover, the extent to which a biosimilar, once approved, will be substituted for any one of our reference products in a way that is similar to traditional generic substitution for non-biological products is not yet clear, and will depend on a number of marketplace and regulatory factors that are still developing. If competitors are able to obtain marketing approval for biosimilars referencing our candidates, if approved, our products may become subject to competition from such biosimilars, with the attendant competitive pressure and potential adverse consequences.

The success of our product candidates will depend significantly on coverage and adequate reimbursement or the willingness of patients to pay for these therapies.

We believe our success depends on obtaining and maintaining coverage and adequate reimbursement for our product candidates, including ITIL-168 for the treatment of metastatic melanoma, and the extent to which patients will be willing to pay out-of-pocket for such products, in the absence of reimbursement for all or part of the cost. In the United States and in other countries, patients who are provided medical treatment for their conditions generally rely on third-party payors to reimburse all or part of the costs associated with their treatment. The availability of coverage and adequacy of reimbursement for our products by third-party payors, including government health care programs (e.g., Medicare, Medicaid, TRICARE), managed care providers, private health insurers, health maintenance organizations, and other organizations is essential for most patients to be able to afford medical services and pharmaceutical products such as our product candidates. Third-party payors often rely upon Medicare coverage policy and payment limitations in setting their own coverage and reimbursement policies. However, decisions regarding the extent of coverage and amount of reimbursement to be provided are made on a payor-by-payor basis. One payor's determination to provide coverage for a drug product does not assure that other payors will also provide coverage, and adequate reimbursement. The principal decisions about reimbursement for new medicines are typically made by the Centers for Medicare & Medicaid Services, or CMS, an agency within the United States. Department of Health and Human Services, or HHS. CMS decides whether and to what extent products will be covered and reimbursed under Medicare and private payors tend to follow CMS to a substantial degree.

Third-party payors determine which products and procedures they will cover and establish reimbursement levels. Even if a third-party payor covers a particular product or procedure, the resulting reimbursement payment rates may not be adequate. Patients who are treated in-office for a medical condition generally rely on third-party payors to reimburse all or part of the costs associated with the procedure, including costs associated with products used during the procedure, and may be unwilling to undergo such procedures in the absence of such coverage and

adequate reimbursement. Physicians may be unlikely to offer procedures for such treatment if they are not covered by insurance and may be unlikely to purchase and use our product candidates, if approved, for our stated indications unless coverage is provided and reimbursement is adequate. In addition, 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.

Reimbursement by a third-party payor may depend upon a number of factors, including the third-party payor's determination that a procedure is safe, effective and medically necessary; appropriate for the specific patient; cost-effective; supported by peer-reviewed medical journals; included in clinical practice guidelines; and neither cosmetic, experimental, nor investigational. Further, increasing efforts by third-party payors in the United States and abroad 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. In order to secure coverage and reimbursement for any product that might be approved for sale, we may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost-effectiveness of our products, in addition to the costs required to obtain FDA or comparable regulatory approvals. Additionally, we may also need to provide discounts to purchasers, private health plans or government healthcare programs. Our product candidates may nonetheless not be considered medically necessary or cost-effective. If third-party payors do not consider a product to be cost-effective compared to other available therapies, they may not cover the product after approval as a benefit under their plans or, if they do, the level of payment may not be sufficient to allow a company to sell its products at a profit. We expect to experience pricing pressures from third-party payors in connection with the potential sale of any of our product candidates. 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 and also have a material adverse effect on sales.

Foreign governments also have their own healthcare reimbursement systems, which vary significantly by country and region, and we cannot be sure that coverage and adequate reimbursement will be made available with respect to the treatments in which our products are used under any foreign reimbursement system.

There can be no assurance that ITIL-168 or any other product candidate, if approved for sale in the United States or in other countries, will be considered medically reasonable and necessary, that it will be considered cost-effective by third-party payors, that coverage or an adequate level of reimbursement will be available or that reimbursement policies and practices in the United States and in foreign countries where our products are sold will not adversely affect our ability to sell our product candidates profitably, if they are approved for sale.

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

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

- decreased demand for any product candidates or drugs that we may develop;
- injury to our reputation and significant negative media attention;
- withdrawal of clinical trial participants;
- significant costs to defend the related litigation;
- substantial monetary awards paid to trial participants or patients;
- loss of revenue;
- reduced resources of our management to pursue our business strategy; and
- the inability to commercialize any products that we may develop.

Although we maintain product liability insurance coverage, such insurance may not be adequate to cover all liabilities that we may incur. We may need to increase our insurance coverage as we expand our clinical trials or if we commence commercialization of our product candidates. Insurance coverage is increasingly expensive. We may not be able to maintain insurance coverage at a reasonable cost or in an amount adequate to satisfy any liability that may arise.

Our business and operations would suffer in the event of computer system failures, cyberattacks or a deficiency in our cybersecurity.

Despite the implementation of security measures, our internal computer systems, and those of third parties on which we rely, are subject to attack by computer viruses, malware, natural disasters, terrorism, war, telecommunication and electrical failures, cyberattacks or cyber-intrusions over the Internet, attachments to emails, persons inside our organization, or persons with access to systems inside our organization and vulnerable to damage therefrom. The risk of a security breach or disruption, particularly through cyberattacks or cyber intrusion, including by computer hackers, foreign governments, and cyber terrorists, has generally increased as the number, intensity and sophistication of attempted attacks and intrusions from around the world have increased. If such an event were to interrupt our operations, it could result in a material disruption of our product development programs. For example, the loss of clinical trial data from completed or ongoing or planned clinical trials could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any disruption or security breach was to result in a loss of or damage to our data or applications, or inappropriate disclosure of confidential or proprietary information, we could incur material legal claims and liability and damage to our reputation, and the further development of our product candidates could be delayed.

We are subject to a variety of privacy and data security laws, and our failure to comply with them could harm our business.

We maintain a large quantity of sensitive information, including confidential business and personal information in connection with the conduct of our clinical trials and related to our employees, and we are subject to laws and regulations governing the privacy and security of such information. In the United States, there are numerous federal and state privacy and data security laws and regulations governing the collection, use, disclosure and protection of personal information, including federal and state health information privacy laws, federal and state security breach notification laws, and federal and state consumer protection laws. The legislative and regulatory landscape for privacy and data protection continues to evolve, and there has been an increasing focus on privacy and data protection issues, which may affect our business and is expected to increase our compliance costs and exposure to liability. In the United States, numerous federal and state laws and regulations could apply to our operations or the operations of our partners, including state data breach notification laws, state health information privacy laws, and federal and state consumer protection laws and regulations (e.g. Section 5 of the FTC Act), that govern the collection, use, disclosure, and protection of health-related and other personal information. In addition, we may obtain health information from third parties (including research institutions from which we obtain clinical trial data) that are subject to privacy and security requirements under the Health Insurance Portability and Accountability Act, or HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, or HITECH, and regulations promulgated thereunder. Depending on the facts and circumstances, we could be subject to significant penalties if we obtain, use, or disclose individually identifiable health information in a manner that is not authorized or permitted by HIPAA.

In Europe, the General Data Protection Regulation or the GDPR, took effect in May 2018. The GDPR governs the collection, use, disclosure, transfer or other processing of personal data of individuals within the European Economic Area, or the EEA, including clinical trial data. Among other things, the GDPR imposes requirements regarding the security of personal data and notification of data processing obligations to the competent national data processing authorities, requires having lawful bases on which personal data can be processed, and requires changes to informed consent practices, as well as more detailed notices for clinical trial subjects and investigators. In addition, the GDPR increases the scrutiny of transfers of personal data from the EEA to the United States and other jurisdictions that the European Commission does not recognize as having “adequate” data protection laws; in July 2020, the Court of Justice of the European Union limited how organizations could lawfully transfer personal data from the EEA to the United States by invalidating the EU-US Privacy Shield and imposing further restrictions on

use of the standard contractual clauses, which could increase our costs and our ability to efficiently process personal data from the EEA. The GDPR imposes substantial fines for breaches and violations (up to the greater of €20 million or 4% of our consolidated annual worldwide gross revenue), and confers a private right of action on data subjects and consumer associations to lodge complaints with supervisory authorities, seek judicial remedies and obtain compensation for damages resulting from violations of the GDPR. Relatedly, following the United Kingdom's withdrawal from the European Economic Area and the European Union, and the expiry of the transition period, which ended on January 1, 2021, companies have to comply with both the GDPR and the GDPR as incorporated into United Kingdom national law, the latter regime having the ability to separately fine up to the greater of £17.5 million or 4% of global turnover. On January 1, 2021, the United Kingdom became a third country for the purposes of the GDPR.

The relationship between the United Kingdom and the European Union in relation to certain aspects of data protection law remains unclear, for example around how data can lawfully be transferred between each jurisdiction, which exposes us to further compliance risk. Pursuant to the EU-UK Trade and Cooperation Agreement of December 24, 2020, transfers of personal data from the European Union to the United Kingdom may continue to take place without a need for additional safeguards during a further transition period, to expire on (1) the date on which an adequacy decision with respect to the United Kingdom is adopted by the EU Commission; or (2) the expiry of four months, which shall be extended by a further two months unless either the European Union or the United Kingdom objects. It remains unclear whether the EU Commission will adopt an adequacy decision with respect to the United Kingdom. In the absence of such decision after the expiry of the additional transition period, we may need to put in place additional safeguards for transfers of personal data from the European Union to the United Kingdom, such as standard contractual clauses approved by the EU Commission.

Compliance with these and any other applicable privacy and data security laws and regulations is a rigorous and time-intensive process, and we may be required to put in place additional mechanisms ensuring compliance with the new data protection rules. If we fail to comply with any such laws or regulations, we may face significant fines and penalties that could adversely affect our business, financial condition and results of operations. Furthermore, the laws are not consistent, and compliance in the event of a widespread data breach is costly. In addition, states are constantly adopting new laws or amending existing laws, requiring attention to frequently changing regulatory requirements. For example, California enacted the California Consumer Privacy Act, or the CCPA, which took effect on January 1, 2020, became enforceable by the California Attorney General on July 1, 2020, and has been dubbed the first "GDPR-like" law in the United States. The CCPA gives California residents expanded rights to access and delete their personal information, opt out of certain personal information sharing and receive detailed information about how their personal information is used by requiring covered companies to provide new disclosures to California consumers (as that term is broadly defined) and provide such consumers new ways to opt-out of certain sales of 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. Further, the California Privacy Rights Act, or the CPRA, recently passed in California. The CPRA will impose additional data protection obligations on companies doing business in California, 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. Although the CCPA currently exempts certain health-related information, including clinical trial data, the CCPA and the CPRA may increase our compliance costs and potential liability. Similar laws have been proposed in other states and at the federal level, and if passed, such laws may have potentially conflicting requirements that would make compliance challenging.

If we or any contract manufacturers and suppliers we engage fail to comply with environmental, health, and safety laws and regulations, we could become subject to fines or penalties or incur costs that could seriously harm our business.

We and any contract manufacturers and suppliers we engage are subject to numerous federal, state and local environmental, health, and safety laws, regulations, and permitting requirements, including those governing

laboratory procedures; the generation, handling, use, storage, treatment and disposal of hazardous and regulated materials and wastes; the emission and discharge of hazardous materials into the ground, air and water; and employee health and safety. Our operations involve the use of hazardous and flammable materials, including chemicals and biological materials. Our operations also produce hazardous waste. We generally contract with third parties for the disposal of these materials and wastes. We cannot eliminate the risk of contamination or injury from these materials. In the event of contamination or injury resulting from our use of hazardous materials, we could be held liable for any resulting damages, and any liability could exceed our resources. Under certain environmental laws, we could be held responsible for costs relating to any contamination at our current or past facilities and at third-party facilities. We also could incur significant costs associated with civil or criminal fines and penalties.

Compliance with applicable environmental laws and regulations may be expensive, and current or future environmental laws and regulations may impair our research, product development and manufacturing efforts. In addition, we cannot entirely eliminate the risk of accidental injury or contamination from these materials or wastes. Although we maintain workers' compensation insurance to cover us for costs and expenses we may incur due to injuries to our employees resulting from the use of hazardous materials, this insurance may not provide adequate coverage against potential liabilities. We do not carry specific biological or hazardous waste insurance coverage, and our property, casualty, and general liability insurance policies specifically exclude coverage for damages and fines arising from biological or hazardous waste exposure or contamination. Accordingly, in the event of contamination or injury, we could be held liable for damages or be penalized with fines in an amount exceeding our resources, and our clinical trials or regulatory approvals could be suspended, which could seriously harm our business.

Risks Related to Our Dependence on Third Parties

We intend to rely on third parties to conduct, supervise and monitor a significant portion of our research and preclinical testing and clinical trials for our product candidates, and if those third parties do not successfully carry out their contractual duties, comply with regulatory requirements or otherwise perform satisfactorily, we may not be able to obtain regulatory approval or commercialize product candidates, or such approval or commercialization may be delayed, and our business may be substantially harmed.

We intend to engage CROs and other third parties to conduct our planned preclinical studies or clinical trials and to monitor and manage data. We expect to continue to rely on third parties, including clinical data management organizations, medical institutions and clinical investigators, to conduct those clinical trials. Any of these third parties may terminate their engagements with us, some in the event of an uncured material breach and some at any time for convenience. If any of our relationships with these third parties terminate, we may not be able to timely enter into arrangements with alternative third parties or to do so on commercially reasonable terms, if at all. Switching or adding CROs involves substantial cost and requires management time and focus. In addition, there is a natural transition period when a new CRO commences work. As a result, delays occur, which can 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 a material adverse impact on our business, financial condition and prospects. Further, the performance of our CROs and other third parties conducting our trials may also be interrupted by the ongoing COVID-19 pandemic, including due to travel or quarantine policies, heightened exposure of CRO or clinical site or other vendor staff who are healthcare providers to COVID-19 or prioritization of resources toward the pandemic.

In addition, any third parties conducting our clinical trials will not be our employees, and except for remedies available to us under our agreements with such third parties, we cannot control whether or not they devote sufficient time and resources to our clinical programs. If these third parties do not successfully carry out their contractual duties or obligations or meet expected deadlines, if they need to be replaced or if the quality or accuracy of the clinical data they obtain is compromised due to the failure to adhere to our clinical protocols, regulatory requirements or for other reasons, our clinical trials may be extended, delayed or terminated and we may not be able to obtain regulatory approval for or successfully commercialize our product candidates. Consequently, our results of operations and the commercial prospects for our product candidates would be harmed, our costs could increase substantially and our ability to generate revenue could be delayed significantly.

We rely on these parties for execution of our preclinical studies and clinical trials, and generally do not control their activities. Our reliance on these third parties for research and development activities will reduce our control over these activities but will not relieve us of our responsibilities. For example, we will remain responsible for ensuring that each of our clinical trials is conducted in accordance with the general investigational plan and protocols for the trial. Moreover, the FDA requires us to comply with standards, commonly referred to as good clinical practices, or GCPs, for conducting, recording and reporting the results of clinical trials to assure that data and reported results are credible and accurate and that the rights, integrity and confidentiality of trial participants are protected. If we or any of our CROs or other third parties, including trial sites, fail to comply with applicable GCPs, the clinical data generated in our clinical trials may be deemed unreliable and the FDA, EMA 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 regulations. In addition, our clinical trials must be conducted with product produced under cGMP conditions. Our failure to comply with these regulations may require us to repeat clinical trials, which would delay the regulatory approval process.

We also are required to register certain ongoing clinical trials and post the results of certain completed clinical trials on a government-sponsored database, ClinicalTrials.gov, within specified timeframes. Failure to do so can result in fines, adverse publicity and civil and criminal sanctions.

In addition, principal investigators for our clinical trials may serve as scientific advisors or consultants to us from time to time and receive compensation in connection with such services. Under certain circumstances, we may be required to report some of these relationships to the FDA. The FDA may conclude that a financial relationship between us and a principal investigator has created a conflict of interest or otherwise affected interpretation of the trial. The FDA may therefore question the integrity of the data generated at the applicable clinical trial site and the utility of the clinical trial itself may be jeopardized. This could result in a delay in approval, or rejection, of our marketing applications by the FDA and may ultimately lead to the denial of marketing approval for ITIL-168, ITIL-306 or any other product candidates.

We also expect to rely on other third parties to store and distribute product supplies for our clinical trials. Any performance failure on the part of our distributors could delay clinical development or marketing approval of our product candidates or commercialization of our products, producing additional losses and depriving us of potential revenue.

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

We may seek third-party collaborators for the development and commercialization of our product candidates, including for the commercialization of any of our product candidates that are approved for marketing outside the United States. Our likely collaborators for any such arrangements include regional and national pharmaceutical companies and biotechnology companies. If we enter into any additional such arrangements with any third parties, we will likely have limited control over the amount and timing of resources that our collaborators dedicate to the development or commercialization of our product candidates. Our ability to generate revenue from these arrangements will depend on our collaborators' abilities to successfully perform the functions assigned to them in these arrangements.

Collaborations involving our product candidates would pose the following risks to us:

- 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 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;
- we could grant exclusive rights to our collaborators that would prevent us from collaborating with others;
- product candidates discovered in collaboration with us may be viewed by our collaborators as competitive with their own product candidates or drugs, which may cause collaborators to cease to devote resources to the commercialization of our product candidates;
- 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 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 maintain or defend our or their intellectual property rights or may use our or their proprietary information in such a way as to invite litigation that could jeopardize or invalidate such intellectual property or proprietary information or expose us to potential litigation;
- collaborators may infringe the intellectual property rights of third parties, which may expose us to litigation and potential liability; and
- collaborations may be terminated for the convenience of the collaborator and, if terminated, we could be required to raise additional capital to pursue further development or commercialization of the applicable product candidates.

Collaboration agreements may not lead to development or commercialization of product candidates in the most efficient manner or at all. If any future collaborator of ours were to be involved in a business combination, the continued pursuit and emphasis on our product development or commercialization program could be delayed, diminished or terminated.

We face significant competition in seeking appropriate collaborators. Whether we reach a definitive agreement for any 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. Those factors may include the design or results of clinical trials, the likelihood of approval by the FDA, EMA or similar regulatory authorities outside the United States, the potential market for the subject product candidate, the costs and complexities of manufacturing and delivering such product candidate to patients, the potential of competing products, the existence of uncertainty with respect to our ownership of technology, which can exist if there is a challenge to such ownership without regard to the merits of the challenge and industry and market conditions generally. The collaborator may also consider alternative product candidates or technologies for similar indications that may be available to collaborate on and whether such a collaboration could be more attractive than the one with us for our product candidate. Collaborations are complex and time-consuming to negotiate and document. In addition, there have been a significant number of recent business combinations among large pharmaceutical companies that have resulted in a reduced number of potential future collaborators.

We may not be able to negotiate additional collaborations on a timely basis, on acceptable terms, or at all. If we are unable to do so, we may have to curtail the development of such 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 increase our expenditures to fund development or commercialization activities on our own, we may need to obtain additional capital, which may not be available to us on acceptable terms or at all. If we do not have sufficient funds, we may not be able to further develop our product candidates or bring them to market and generate revenue.

Risks Related to our Intellectual Property

If we are unable to obtain or protect intellectual property rights related to any of our product candidates, we may not be able to compete effectively in our market.

We rely upon a combination of patents, trade secret protection and confidentiality agreements to protect the intellectual property related to our product candidates and technologies. Our success depends in large part on our ability to obtain and maintain patent and other intellectual property protection in the United States and in other countries with respect to our proprietary technology and product candidates.

As of the date of this Annual Report on Form 10-K, we do not currently in-license any intellectual property, but we may choose to do so in the future. The strength of patents in the biotechnology and pharmaceutical field involves complex legal and scientific questions and can be uncertain. We cannot offer any assurances about which of our patent applications will issue, the breadth of any resulting patent or whether any of the issued patents will be found invalid and unenforceable or will be threatened by third parties. We cannot offer any assurances that the breadth of our resulting or granted patents will be sufficient to stop a competitor from developing and commercializing a product, including a biosimilar product, that would be competitive with one or more of our product candidates. There is no assurance that all the potentially relevant prior art relating to our patent and patent applications has been found, which can invalidate a patent or prevent a patent from issuing from a pending patent application. Since patent applications in the United States and most other countries are confidential for a period of time after filing, we cannot be certain that we or our future licensors were the first to file any patent application related to our product candidates and technologies. Additionally, a derivation proceeding before the United States Patent and Trademark Office can be initiated by a third party to contest inventorship of the subject matter claimed in our applications.

Furthermore, any successful challenge to these patents or any other patents owned by or licensed to us after patent issuance could deprive us of rights necessary for the successful commercialization of any of our product candidates and technologies that we may develop. Even if they are unchallenged or such third-party challenges are unsuccessful, our patent and patent applications may not adequately protect our intellectual property, provide exclusivity for our product candidates and technologies, or prevent others from designing around our claims. If the breadth or strength of protection provided by the patent and patent applications we hold, obtain or pursue with respect to our product candidates and technologies is challenged, or if they fail to provide meaningful exclusivity for our product candidates and technologies, it could threaten our ability to commercialize our product candidates and technologies. Further, if we encounter delays in regulatory approvals, the period of time during which we could market a product candidate under patent protection, if approved, would be reduced.

The patent prosecution process is expensive and time-consuming. We may not be able to prepare, file and prosecute all necessary or desirable patent applications at a commercially reasonable cost, in a timely manner, or in all jurisdictions. It is also possible that we may fail to identify patentable aspects of inventions made in the course of development and commercialization activities before it is too late to obtain patent protection. Moreover, depending on the terms of any future in-licenses to which we may become a party, we may not have the right to control the preparation, filing and prosecution of patent applications, or to maintain the patents, covering technology in-licensed from third parties. Therefore, these patents and patent applications may not be prosecuted and enforced in a manner consistent with the best interests of our business. In addition to the protection provided by our patent estate, we rely on trade secret protection and confidentiality agreements to protect proprietary scientific, business and technical information and know-how that is not or may not be patentable or that we elect not to patent. We seek to protect our proprietary information, data and processes, in part, by confidentiality agreements and invention assignment agreements with our employees, consultants, scientific advisors, contractors and partners. Although these

agreements are designed to protect our proprietary information, we cannot be certain that our trade secrets and other confidential proprietary information will not be disclosed or that competitors will not otherwise gain access to our trade secrets or independently develop substantially equivalent information and techniques. Although we generally require all of our employees to assign their inventions to us, and all of our employees, consultants, advisors and any third parties who have access to our proprietary know-how, information, or technology to enter into confidentiality agreements, we cannot provide any assurances that all such agreements have been duly executed with all third parties who may have helped to develop our intellectual property or who had access to our proprietary information, or that our agreements will not be breached. If any of the parties to these confidentiality agreements breaches or violates the terms of such agreements, we may not have adequate remedies for any such breach or violation, and we could lose our trade secrets as a result.

Enforcing a claim that a third party illegally obtained and is using our trade secrets, like patent litigation, is expensive and time-consuming, and the outcome is unpredictable. Further, the laws of some foreign countries do not protect proprietary rights to the same extent or in the same manner as the laws of the United States. The enforceability of confidentiality agreements may vary from jurisdiction to jurisdiction. As a result, we may encounter significant problems in protecting and defending our intellectual property both in the United States and abroad. Additionally, if the steps taken to maintain our trade secrets are deemed inadequate, we may have insufficient recourse against third parties for misappropriating the trade secret. We cannot guarantee that our employees, former employees or consultants will not file patent applications claiming our inventions. Because of the "first-to-file" laws in the United States and the uncertainties surrounding outcomes of derivation proceedings before the United States Patent and Trademark Office, such unauthorized patent application filings may defeat our attempts to obtain patents on our own inventions.

Trade secrets and know-how can be difficult to protect as trade secrets and know-how will over time be disseminated within the industry through independent development, the publication of journal articles, and the movement of personnel skilled in the art from company to company or academic to industry scientific positions. Moreover, our competitors may independently develop knowledge, methods and know-how equivalent to our trade secrets. Competitors could purchase our products and attempt to replicate some or all of the competitive advantages we derive from our development efforts, willfully infringe our intellectual property rights, design around our protected technology or develop their own technologies that fall outside of our intellectual property rights. If any of our trade secrets were to be lawfully obtained or independently developed by a competitor, we would have no right to prevent them, or those to whom they communicate it, from using that technology or information to compete with us. If any of our trade secrets and proprietary know-how were to be disclosed to or independently developed by a competitor, our competitive position would be harmed.

We also seek to preserve the integrity and confidentiality of our data and trade secrets by maintaining physical security of our premises and physical and electronic security of our information technology systems. Monitoring unauthorized uses and disclosures is difficult, and we do not know whether the steps we have taken to protect our proprietary technologies will be effective.

While we have confidence in these individuals, organizations and systems, our agreements or security measures may be breached, and we may not have adequate remedies for any breach. Also, if the steps taken to maintain our trade secrets are deemed inadequate, we may have insufficient recourse against third parties for misappropriating the trade secret. In addition, others may independently discover our trade secrets and proprietary information. For example, the FDA is considering whether to make additional information publicly available on a routine basis, including information that we may consider to be trade secrets or other proprietary information, and it is not clear at the present time how the FDA's disclosure policies may change in the future. If we are unable to prevent material disclosure of the non-patented intellectual property related to our technologies to third parties, and there is no guarantee that we will have any such enforceable trade secret protection, we may not be able to establish or maintain a competitive advantage in our market, which could materially adversely affect our business, results of operations and financial condition.

Patent terms may be inadequate to protect our competitive position on our products for an adequate amount of time, and if we do not obtain protection under the Hatch-Waxman Amendments and similar non-United States legislation for extending the term of patents covering each of our product candidates, our business may be materially harmed.

Patents have a limited lifespan. In the United States, the natural expiration of a patent is generally 20 years after its first effective filing date. Although various extensions may be available, the life of a patent, and the protection it affords, is limited. Even if patents covering our product candidates are obtained, once the patent life has expired for a product, we may be open to competition from generic medications. Given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such candidates may expire before or shortly after such candidates are commercialized. Depending upon the timing, duration and conditions of FDA marketing approval of our product candidates, one or more of our United States patents may be eligible for limited patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984, referred to as the Hatch-Waxman Amendments, and similar legislation in the European Union. The Hatch-Waxman Amendments permit 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. A 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 may be extended, and only those claims covering the approved drug, a method for using it, or a method for manufacturing it may be extended. However, we may not receive an extension if we fail to apply within applicable deadlines, fail to apply prior to expiration of relevant patents or otherwise fail to satisfy applicable requirements. Moreover, the length of the extension could be less than we request. If we are unable to obtain patent term extension or the term of any such extension is less than we request, the period during which we can enforce our patent rights for that product will be shortened and our competitors may obtain approval to market competing products sooner. As a result, our revenue from applicable products could be reduced and could have a material adverse effect on our business.

If we fail to comply with our obligations imposed by any intellectual property licenses with third parties that we may need in the future, we could lose rights that are important to our business.

Although we do not currently have any intellectual property licenses with third parties, we may in the future require licenses to additional third-party technology and materials. Such licenses may not be available in the future or may not be available on commercially reasonable terms, or at all, which could have a material adverse effect on our business and financial condition. Even if we acquire the right to control the prosecution, maintenance and enforcement of the licensed and sublicensed intellectual property relating to our product candidates, we may require the cooperation of our licensors and any upstream licensor, which may not be forthcoming. Therefore, we cannot be certain that the prosecution, maintenance and enforcement of these patent rights will be in a manner consistent with the best interests of our business. If we or our licensor fail to maintain such patents, or if we or our licensor lose rights to those patents or patent applications, the rights we have licensed may be reduced or eliminated and our right to develop and commercialize any of our product candidates that are the subject of such licensed rights could be adversely affected. In addition to the foregoing, the risks associated with patent rights that we license from third parties will also apply to patent rights we may own in the future. Further, if we fail to comply with our development obligations under our license agreements, we may lose our patent rights with respect to such agreement, which would affect our patent rights worldwide.

Termination of our current or any future license agreements would reduce or eliminate our rights under these agreements and 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. Any of the foregoing could prevent us from commercializing our other product candidates, which could have a material adverse effect on our operating results and overall financial condition.

In addition, intellectual property rights that we in-license in the future may be sublicenses under intellectual property owned by third parties, in some cases through multiple tiers. The actions of our licensors may therefore affect our rights to use our sublicensed intellectual property, even if we are in compliance with all of the obligations under our license agreements. Should our licensors or any of the upstream licensors fail to comply with their obligations under the agreements pursuant to which they obtain the rights that are sublicensed to us, or should such agreements be terminated or amended, our ability to develop and commercialize our product candidates may be materially harmed.

Patent reform legislation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our future patents.

Our ability to obtain patents is highly uncertain because, to date, some legal principles remain unresolved, and there has not been a consistent policy regarding the breadth or interpretation of claims allowed in patents in the United States. Furthermore, the specific content of patents and patent applications that are necessary to support and interpret patent claims is highly uncertain due to the complex nature of the relevant legal, scientific, and factual issues. Changes in either patent laws or interpretations of patent laws in the United States and other countries may diminish the value of our intellectual property or narrow the scope of our patent protection.

For example, on September 16, 2011, the Leahy-Smith America Invents Act, or the Leahy-Smith Act, was signed into law. The Leahy-Smith Act included a number of significant changes to United States patent law. These included provisions that affect the way patent applications will be prosecuted and may also affect patent litigation. The USPTO has developed new and untested regulations and procedures to govern the full implementation of the Leahy-Smith Act, and many of the substantive changes to patent law associated with the Leahy-Smith Act, and in particular, the first to file provisions, became effective in March 2013. The Leahy-Smith Act has also introduced procedures making it easier for third parties to challenge issued patents, as well as to intervene in the prosecution of patent applications. Finally, the Leahy-Smith Act contained new statutory provisions that require the USPTO to issue new regulations for their implementation, and it may take the courts years to interpret the provisions of the new statute. It is too early to tell what, if any, impact the Leahy-Smith Act will have on the operation of our business and the protection and enforcement of our intellectual property. However, the Leahy-Smith Act and its implementation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of our future patents. Further, the United States Supreme Court has ruled on several patent cases in recent years, either narrowing the scope of patent protection available in certain circumstances or weakening the rights of patent owners in certain situations. In addition to increasing uncertainty with regard to our ability to obtain patents in the future, this combination of events has created uncertainty with respect to the value of patents, once obtained. Depending on actions by the United States Congress, the federal courts and the USPTO, the laws and regulations governing patents could change in unpredictable ways that would weaken our ability to obtain new patents or to enforce patents that we have owned or licensed or that we might obtain in the future. An inability to obtain, enforce, and defend patents covering our proprietary technologies would materially and adversely affect our business prospects and financial condition.

Similarly, changes in patent laws and regulations in other countries or jurisdictions, changes in the governmental bodies that enforce them or changes in how the relevant governmental authority enforces patent laws or regulations may weaken our ability to obtain new patents or to enforce patents that we may obtain in the future. Further, the laws of some foreign countries do not protect proprietary rights to the same extent or in the same manner as the laws of the United States. As a result, we may encounter significant problems in protecting and defending our intellectual property both in the United States and abroad. For example, if the issuance in a given country of a patent covering an invention is not followed by the issuance in other countries of patents covering the same invention, or if any judicial interpretation of the validity, enforceability or scope of the claims or the written description or enablement, in a patent issued in one country is not similar to the interpretation given to the corresponding patent issued in another country, our ability to protect our intellectual property in those countries may be limited. Changes in either patent laws or in interpretations of patent laws in the United States and other countries may materially diminish the value of our intellectual property or narrow the scope of our patent protection.

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

Competitors may infringe our issued patents or any patents issued as a result of our pending or future patent applications. To counter infringement or unauthorized use, we may be required to file infringement claims, which can be expensive and time-consuming. In addition, in an infringement proceeding, a court may decide that a patent of ours is not valid or is unenforceable, or may refuse to stop the other party in such infringement proceeding from using the technology at issue on the grounds that our patents do not cover the technology in question. An adverse result in any litigation or defense proceedings could put one or more of our patents at risk of being invalidated, held

unenforceable or interpreted narrowly, and could put any of our patent applications at risk of not yielding an issued patent.

If we initiate legal proceedings against a third party to enforce a patent covering one of our product candidates, the defendant could counterclaim that the patent covering our product or product candidate is invalid and/or unenforceable. In patent litigation in the United States, counterclaims alleging invalidity and/or unenforceability are common, and there are numerous grounds upon which a third party can assert invalidity or unenforceability of a patent. Grounds for a validity challenge could be an alleged failure to meet any of several statutory requirements, including lack of novelty, obviousness or non-enablement. Grounds for an unenforceability assertion could be an allegation that someone connected with prosecution of the patent withheld relevant information from the PTO, or made a misleading statement, during prosecution. Third parties may also raise similar claims before administrative bodies in the United States or abroad, even outside the context of litigation. Such mechanisms include re-examination, post grant review, *inter partes* review and equivalent proceedings in foreign jurisdictions (for example, opposition proceedings, nullity proceedings or litigation or invalidation trials or invalidation proceedings). Such proceedings could result in revocation of or amendment to our patents in such a way that they no longer cover our product candidates. The outcome following legal assertions of invalidity and unenforceability is unpredictable. With respect to the validity of our patents, for example, we cannot be certain that there is no invalidating prior art of which we, our patent counsel, and the patent examiner were unaware during prosecution. If a defendant were to prevail on a legal assertion of invalidity and/or unenforceability, we would lose at least part, and perhaps all, of the patent protection on our product candidates. An adverse result in any litigation or defense proceedings could put one or more of our patents at risk of being invalidated or interpreted narrowly, could put our patent applications at risk of not issuing and could have a material adverse impact on our business.

Derivation proceedings initiated by third parties or us may be necessary to determine the inventorship (and possibly also ownership) of inventions with respect to our patent applications or resulting patents, or patent applications or resulting patents of third parties. An unfavorable outcome could require us to cease using the related technology or force us to take a license under the patent rights of the prevailing party, if available. Furthermore, our business could be harmed if the prevailing party does not offer us a license on commercially reasonable terms. Our defense of litigation or interference proceedings may fail and, even if successful, may result in substantial costs and distract our management and other employees. We may not be able to prevent misappropriation of our intellectual property rights, particularly in countries where the laws may not protect those rights as fully as in the United States.

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

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

We cannot guarantee that any of our patent searches or analyses, including the identification of relevant patents, the scope and validity 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 and abroad that is relevant to or necessary for the commercialization of our product candidates in any jurisdiction.

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

We may be unsuccessful in licensing or acquiring intellectual property from third parties that may be required to develop and commercialize our product candidates.

A third party may hold intellectual property, including patent rights that are important or necessary to the development and commercialization of our product candidates. It may be necessary for us to use the patented or proprietary technology of third parties to commercialize our product candidates, in which case we would be required to acquire or obtain a license to such intellectual property from these third parties, and we may be unable to do so on commercially reasonable terms or 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. We also may be unable to license or acquire third-party intellectual property rights on terms that would allow us to make an appropriate return on our investment or at all. If we are unable to successfully obtain rights to required third-party intellectual property rights or maintain the existing intellectual property rights we have, we may have to abandon development of the relevant program or product candidate, which could have a material adverse effect on our business.

Third parties may initiate legal proceedings alleging that we are infringing their intellectual property rights, the outcome of which would be uncertain.

Our commercial success depends in part on our ability to develop, manufacture, market and sell our drug candidates and use our proprietary technologies without infringing or otherwise violating the patents and proprietary rights of third parties. As our current and future product candidates progress toward commercialization, the possibility of a patent infringement claim against us increases. There is a substantial amount of litigation involving patent and other intellectual property rights in the biotechnology and pharmaceutical industries, including patent infringement lawsuits, interferences, derivation proceedings, post grant reviews, inter partes reviews, and reexamination proceedings before the USPTO or oppositions and other comparable proceedings in foreign jurisdictions. Numerous United States 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 there may be third-party patents or patent applications with claims to materials, formulations, methods of manufacture or methods for treatment related to the use or manufacture of our product candidates and technologies. Third parties, including our competitors may initiate legal proceedings against us alleging that we are infringing or otherwise violating their patent or other intellectual property rights.

We cannot provide any assurance that our current and future product candidates do not infringe other parties' patents or other proprietary rights, and competitors or other parties may assert that we infringe their proprietary rights in any event. We may become party to, or threatened with, adversarial proceedings or litigation regarding intellectual property rights with respect to our current and future product candidates, including interference or derivation proceedings before the USPTO. Even if we believe such claims are without merit, a court of competent jurisdiction could hold that these third-party patents are valid, enforceable and infringed, which could have a negative impact on our ability to commercialize ITIL-168, ITIL-306 or any future product candidates. In order to successfully challenge the validity of any such United States patent in federal court, we would need to overcome a presumption of validity. As this burden is high and requires us to present clear and convincing evidence as to the invalidity of any such United States patent claim, there is no assurance that a court of competent jurisdiction would agree with us and invalidate the claims of any such United States patent. Moreover, given the vast number of patents in our field of technology, we cannot be certain that we do not infringe existing patents or that we will not infringe patents that may be granted in the future.

While we may decide to initiate proceedings to challenge the validity of these or other patents in the future, we may be unsuccessful, and courts or patent offices in the United States and abroad could uphold the validity of any such patent. Furthermore, because patent applications can take many years to issue and may be confidential for 18 months or more after filing, and because pending patent claims can be revised before issuance, there may be

applications now pending which may later result in issued patents that may be infringed by the manufacture, use or sale of our product candidates. Regardless of when filed, we may fail to identify relevant third-party patents or patent applications, or we may incorrectly conclude that a third-party patent is invalid or not infringed by our product candidates or activities. If a patent holder believes that one of our product candidates infringes its patent, the patent holder may sue us even if we have received patent protection for our technology. In addition, third parties may obtain patents in the future and claim that our product candidates or technologies infringe upon these patents. Moreover, we may face patent infringement claims from non-practicing entities that have no relevant drug revenue and against whom our own patent portfolio may thus have no deterrent effect. If a patent infringement suit were threatened or brought against us, we could be forced to stop or delay research, development, manufacturing or sales of the drug or product candidate that is the subject of the actual or threatened suit.

If we are found to infringe a third party's valid intellectual property rights, we could be required to obtain a license from such third party to continue commercializing our product candidates. However, we may not be able to obtain any required license on commercially reasonable terms or at all. Even if a license can be obtained on acceptable terms, the rights may be non-exclusive, which could give our competitors access to the same technology or intellectual property rights licensed to us. If we fail to obtain a required license, we may be unable to effectively market product candidates based on our technology, which could limit our ability to generate revenue or achieve profitability and possibly prevent us from generating revenue sufficient to sustain our operations. Alternatively, we may need to redesign our infringing products, which may be impossible or require substantial time and monetary expenditure. Under certain circumstances, we could be forced, including by court orders, to cease commercializing our product candidates. In addition, in any such proceeding or litigation, we could be found liable for substantial monetary damages, potentially including treble damages and attorneys' fees, if we are found to have willfully infringed the patent at issue. A finding of infringement could prevent us from commercializing our product candidates or force us to cease some of our business operations, which could harm our business. Any claims by third parties that we have misappropriated their confidential information or trade secrets could have a similar negative impact on our business.

The cost to us in defending or initiating any litigation or other proceeding relating to patent or other proprietary rights, even if resolved in our favor, could be substantial, and litigation would divert our management's attention. Some of our competitors may be able to sustain the costs of complex patent litigation more effectively than we can because they have substantially greater resources. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could delay our research and development efforts and limit our ability to continue our operations.

We may be subject to claims that our employees, consultants, or independent contractors have wrongfully used or disclosed confidential information of third parties.

We employ individuals who were previously employed at other biotechnology or biopharmaceutical companies. Although we try to ensure that our employees, consultants and advisors do not use the proprietary information or know-how of others in their work for us, we may be subject to claims that 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 future patents. Litigation may be necessary to defend against these claims. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights or personnel. There is no guarantee of success in defending these claims, and even if we are successful, litigation could result in substantial cost and be a distraction to our management and other employees.

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

We may also be subject to claims that former employees, collaborators, or other third parties have an ownership interest in our patent applications, our future patents issued as a result of our pending or future applications, or other intellectual property. We may be subject to ownership disputes in the future arising, for example, from conflicting obligations of consultants or others who are involved in developing our product

candidates. Although it is our policy to require our employees and contractors who may be involved in the conception or development of intellectual property to execute agreements assigning such intellectual property to us, we may be unsuccessful in executing such an agreement with each party who, in fact, conceives or develops intellectual property that we regard as our own, and we cannot be certain that our agreements with such parties will be upheld in the face of a potential challenge, or that they will not be breached, for which we may not have an adequate remedy. The assignment of intellectual property rights may not be self-executing or the assignment agreements may be breached, and litigation may be necessary to defend against these and other claims challenging inventorship or ownership. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights, such as exclusive ownership of, or right to use, valuable intellectual property. Such an outcome could have a material adverse effect on our business. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management and other employees.

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

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

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

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

Filing and prosecuting patent applications and defending patents covering our product candidates in all countries throughout the world would be prohibitively expensive. Competitors may use our technologies in jurisdictions where we have not obtained patent protection to develop their own products and, further, may export otherwise infringing products to territories where we have patent protection, but enforcement rights are not as strong as that in the United States or Europe. These products may compete with our product candidates, and our future 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 before they are granted. The examination of each national or regional patent application is an independent proceeding. As a result, patent applications in the same family may issue as patents in some jurisdictions, such as in the United States, but may issue as patents with claims of different scope or may even be refused in other jurisdictions. It is also quite common that depending on the country, the scope of patent protection may vary for the same product candidate or technology.

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 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 from others in those jurisdictions.

The laws of some jurisdictions do not protect intellectual property rights to the same extent as the laws or rules and regulations in the United States and Europe and many companies have encountered significant difficulties in protecting and defending such rights in such jurisdictions. The legal systems of certain countries, particularly certain developing countries, do not favor the enforcement of patents, trade secrets, and other intellectual property rights, especially those relating to life sciences, which could make it difficult for us to stop the infringement of our future patents or marketing of competing products in violation of our proprietary rights generally. In addition, many countries limit the enforceability of patents against third parties, including government agencies or government contractors. In these countries, patents may provide limited or no benefit. Moreover, our ability to protect and enforce our intellectual property rights may be adversely affected by unforeseen changes in foreign intellectual property laws.

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

Some countries also have compulsory licensing laws under which a patent owner may be compelled to grant licenses to third parties. In addition, some countries limit the enforceability of patents against government agencies or government contractors. In those countries, the patent owner may have limited remedies, which could materially diminish the value of such patents. If we are forced to grant a license to third parties with respect to any patents relevant to our business, our competitive position may be impaired.

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

Periodic maintenance fees, renewal fees, annuity fees and various other government fees on patents and/or applications will be due to be paid to the USPTO and various government patent agencies outside of the United States over the lifetime of our patents and/or applications and any patent rights we may obtain in the future. Furthermore, the USPTO and various non-United States government patent agencies require compliance with several procedural, documentary, fee payment and other similar provisions during the patent application process. We employ reputable law firms and other professionals and rely on such third parties to help us comply with these requirements and effect payment of these fees with respect to the patent and patent applications that we own, and if we in-license intellectual property, we may have to rely upon our licensors to comply with these requirements and effect payment of these fees with respect to any patents and patent applications that we license. In many cases, an

inadvertent lapse of a patent or patent application can be cured by payment of a late fee or by other means in accordance with the applicable rules. There are situations, however, in which non-compliance can result in abandonment or lapse of the patents or patent applications, resulting in partial or complete loss of patent rights in the relevant jurisdiction. In such an event, potential competitors might be able to enter the market, which could have a material adverse effect on our business.

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

We expect to rely on trademarks as one means to distinguish our product candidates, if approved for marketing, from the drugs of our competitors. Once we select new trademarks and apply to register them, our trademark applications may not be approved. Although we would be given an opportunity to respond to those rejections, we may be unable to overcome such rejections. Third parties may oppose or attempt to cancel our trademark applications or trademarks, or otherwise challenge our use of the trademarks. In the event that our trademarks are successfully challenged, we could be forced to rebrand our drugs, which could result in loss of brand recognition and could require us to devote resources to advertising and marketing new brands. Our competitors may infringe or otherwise violate our trademarks and we may not have adequate resources to enforce our trademarks. Any of the foregoing events may have a material adverse effect on our business. Moreover, any name we propose to use with our product candidates in the United States must be approved by the FDA, regardless of whether we have registered it, or applied to register it, as a trademark. The FDA typically conducts a review of proposed product names, including an evaluation of potential for confusion with other product names. If the FDA objects to any of our proposed proprietary product names, we may be required to expend significant additional resources in an effort to identify a suitable substitute name that would qualify under applicable trademark laws, not infringe the existing rights of third parties and be acceptable to the FDA.

Any collaboration arrangements that we may enter into in the future may not be successful, which could adversely affect our ability to develop and commercialize our product candidates.

We may seek collaboration arrangements with pharmaceutical or biotechnology companies for the development or commercialization of our product candidates depending on the merits of retaining commercialization rights for ourselves as compared to entering into collaboration arrangements. We will face, to the extent that we decide to enter into collaboration agreements, significant competition in seeking appropriate collaborators. Moreover, collaboration arrangements are complex and time-consuming to negotiate, document, implement and maintain. We may not be successful in our efforts to establish and implement collaborations or other alternative arrangements should we so chose to enter into such arrangements. The terms of any collaborations or other arrangements that we may establish may not be favorable to us.

Any future collaborations that we enter into may not be successful. The success of our collaboration arrangements will depend heavily on the efforts and activities of our collaborators. Collaborations are subject to numerous risks, which may include that:

- collaborators have significant discretion in determining the efforts and resources that they will apply to collaborations;
- collaborators may not pursue development and commercialization of our product candidates or may elect not to continue or renew development or commercialization programs based on clinical trial results, changes in their strategic focus due to the acquisition of competitive products, availability of funding or other external factors, such as a business combination that diverts resources or creates competing priorities;
- collaborators may delay clinical trials, provide insufficient funding for a clinical trial program, stop a clinical trial, abandon a product candidate, repeat or conduct new clinical trials or require a new formulation of a product candidate for clinical testing;
- collaborators could independently develop, or develop with third parties, products that compete directly or indirectly with our products or product candidates;

- a collaborator with marketing, manufacturing and distribution rights to one or more products may not commit sufficient resources to or otherwise not perform satisfactorily in carrying out these activities;
- we could grant exclusive rights to our collaborators that would prevent us from collaborating with others;
- collaborators may not properly maintain or defend our intellectual property rights or may use our intellectual property or proprietary information in a way that gives rise to actual or threatened litigation that could jeopardize or invalidate our intellectual property or proprietary information or expose us to potential liability;
- disputes may arise between us and a collaborator that causes the delay or termination of the research, development or commercialization of our current or future products or that results in costly litigation or arbitration that diverts management attention and resources;
- collaborations may be terminated, and, if terminated, may result in a need for additional capital to pursue further development or commercialization of the applicable current or future products;
- collaborators may own or co-own intellectual property covering our products that results from our collaborating with them, and in such cases, we would not have the exclusive right to develop or commercialize such intellectual property; and
- a collaborator's sales and marketing activities or other operations may not be in compliance with applicable laws resulting in civil or criminal proceedings.

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

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

- others may be able to make products that are similar to or otherwise competitive with our product candidates but that are not covered by the claims of our current or future patents;
- an in-license necessary for the manufacture, use, sale, offer for sale or importation of one or more of our product candidates may be terminated by the licensor;
- we or future collaborators might not have been the first to make the inventions covered by our issued or future issued patents or our pending patent applications;
- we or future collaborators might not have been the first to file patent applications covering certain of our inventions;
- others may independently develop similar or alternative technologies or duplicate any of our technologies without infringing our intellectual property rights;
- it is possible that our pending patent applications will not lead to issued patents;
- issued patents that we own or in-license may be held invalid or unenforceable as a result of legal challenges by our competitors;
- issued patents that we own or in-license may not provide coverage for all aspects of our product candidates in all countries;
- our competitors might conduct research and development activities in countries where we do not have patent rights and then use the information learned from such activities to develop competitive products for sale in our major commercial markets;
- we may not develop additional proprietary technologies that are patentable; and
- the patents of others may have an adverse effect on our business.

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

Risks Related to Legal and Regulatory Compliance Matters

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

Healthcare providers, including physicians, and third-party payors in the United States and elsewhere will play a primary role in the recommendation and prescription of any product candidates for which we obtain marketing approval. Our current and future arrangements with healthcare professionals, principal investigators, consultants, customers and third-party payors subject us to various federal and state fraud and abuse laws and other healthcare laws, including, without limitation, the federal Anti-Kickback Statute, the federal civil and criminal false claims laws and the law commonly referred to as the Physician Payments Sunshine Act and regulations promulgated under such laws. These laws will impact, among other things, our clinical research, proposed sales, marketing and educational programs, and other interactions with healthcare professionals. In addition, we may be subject to patient privacy laws by both the federal government and the states in which we conduct or may conduct our business. The laws that will affect our operations include, but are not limited to:

- the federal Anti-Kickback Statute, which prohibits, among other things, individuals or entities from knowingly and willfully soliciting, receiving, offering or paying any remuneration (including any kickback, bribe or rebate), directly or indirectly, overtly or covertly, in cash or in kind in return for, or to induce, either the referral of an individual, or the purchase, lease, order or arrangement for or recommendation of the purchase, lease, order or arrangement for any good, facility, item or service for which payment may be made, in whole or in part, under a federal healthcare program, such as the Medicare and Medicaid programs. The term “remuneration” has been broadly interpreted to include anything of value. Although there are a number of statutory exceptions and regulatory safe harbors protecting some common activities from prosecution, the exceptions and safe harbors are drawn narrowly. Practices that involve remuneration that may be alleged to be intended to induce prescribing, purchases or recommendations may be subject to scrutiny if they do not qualify for an exception or safe harbor. A person does not need to have actual knowledge of this statute or specific intent to violate it in order to have committed a violation;

- the federal civil and criminal false claims laws, including, without limitation, the federal False Claims Act, which can be enforced by private citizens through civil whistleblower or qui tam actions, and civil monetary penalty laws which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, claims for payment or approval from the federal government, including Medicare, Medicaid and other government payors, that are false or fraudulent or knowingly making, using or causing to be made or used a false record or statement material to a false or fraudulent claim or to avoid, decrease or conceal an obligation to pay money to the federal government. A claim includes “any request or demand” for money or property presented to the United States federal government. Several pharmaceutical and other healthcare companies have been prosecuted under these laws for allegedly providing free product to customers with the expectation that the customers would bill federal programs for the product. Other companies have been prosecuted for causing false claims to be submitted because of the companies’ marketing of products for unapproved, and thus non-reimbursable, uses. In addition, the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the federal False Claims Act;

- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which created additional federal criminal statutes which prohibit, among other things, a person from knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program,

including private third-party payors and knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false, fictitious or fraudulent statement in connection with the delivery of or payment for healthcare benefits, items or services. Similar to the federal Anti-Kickback Statute, a person or entity does not need to have actual knowledge of the statute or specific intent to violate it in order to have committed a violation;

- the federal transparency laws, including the federal Physician Payments Sunshine Act, which requires certain manufacturers of drugs, medical devices, biologicals and medical supplies for which payment is available under Medicare, Medicaid or the State Children's Health Insurance Program, with specific exceptions, to report annually to the Centers for Medicare & Medicaid Services, or CMS, information related to: (i) payments or other "transfers of value'' made to physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors), other health care professionals (such as physician assistants and nurse practitioners), and teaching hospitals, and (ii) ownership and investment interests held by physicians and their immediate family members; and

- analogous state and foreign laws and regulations; state laws that require manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers, marketing expenditures or drug pricing; state laws that require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government, or that otherwise restrict payments that may be made to healthcare providers; and state and local laws that require the registration of pharmaceutical sales representatives.

Because of the breadth of these laws and the narrowness of the statutory exceptions and regulatory safe harbors available, it is possible that some of our business activities could be subject to challenge under one or more of such laws. It is possible that governmental authorities will conclude that our business practices may not comply with current or future statutes, regulations or case law involving applicable fraud and abuse or other healthcare laws and regulations. If our operations are found to be in violation of any of these laws or any other governmental regulations that may apply to us, we may be subject to significant penalties, including, without limitation, civil, criminal and administrative penalties, damages, fines, disgorgement, imprisonment, exclusion from participating in federal and state funded healthcare programs, such as Medicare and Medicaid, additional reporting requirements and oversight if we become subject to a corporate integrity agreement or similar agreement to resolve allegations of non-compliance with these laws, contractual damages, diminished profits and future earnings, reputational harm and the curtailment or restructuring of our operations, any of which could harm our business.

The risk of our being found in violation of these laws is increased by the fact that many of them have not been fully interpreted by the regulatory authorities or the courts, and their provisions are open to a variety of interpretations. Efforts to ensure that our business arrangements with third parties will comply with applicable healthcare laws and regulations will involve substantial costs. Any action against us for violation of these laws, even if we successfully defend against it, could cause us to incur significant legal expenses and divert our management's attention from the operation of our business. The shifting compliance environment and the need to build and maintain robust and expandable systems to comply with multiple jurisdictions with different compliance and/or reporting requirements increases the possibility that a healthcare company may run afoul of one or more of the requirements.

Even if we obtain regulatory approval for ITIL-168, ITIL-306 or any future product candidates, they will remain subject to ongoing regulatory oversight, which may result in significant additional expense.

Even if we obtain any regulatory approval for ITIL-168, ITIL-306 or any future product candidates, such product candidates, they will be subject to ongoing regulatory requirements applicable to manufacturing, labeling, packaging, storage, advertising, promoting, sampling, record-keeping and submission of safety and other post-market information, among other things. Any regulatory approvals that we receive for ITIL-168, ITIL-306 or any future product candidates may also be subject to a risk evaluation and mitigation strategy, limitations on the approved indicated uses for which the drug may be marketed or to the conditions of approval, or requirements that we conduct potentially costly post-marketing testing and surveillance studies, including Phase 4 trials and

surveillance to monitor the quality, safety and efficacy of the drug. An unsuccessful post-marketing study or failure to complete such a study could result in the withdrawal of marketing approval. We will further be required to immediately report any serious and unexpected adverse events and certain quality or production problems with our products to regulatory authorities along with other periodic reports.

Any new legislation addressing drug safety issues could result in delays in product development or commercialization, or increased costs to assure compliance. We will also have to comply with requirements concerning advertising and promotion for our products. Promotional communications with respect to prescription drug products are subject to a variety of legal and regulatory restrictions and must be consistent with the information in the product's approved label. As such, we will not be allowed to promote our products for indications or uses for which they do not have approval, commonly known as off-label promotion. The holder of an approved BLA must submit new or supplemental applications and obtain prior approval for certain changes to the approved product, product labeling, or manufacturing process. A company that is found to have improperly promoted off-label uses of their products may be subject to significant civil, criminal and administrative penalties.

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

If we fail to comply with applicable regulatory requirements following approval of ITIL-168, ITIL-306 or any future product candidates, a regulatory authority may:

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

Any government investigation of alleged violations of law could require us to expend significant time and resources in response and could generate negative publicity. The occurrence of any event or penalty described above may inhibit our ability to commercialize ITIL-168, ITIL-306 or any future product candidates and harm our business, financial condition, results of operations and prospects.

Even if we obtain FDA or EMA approval any of our product candidates in the United States or European Union, we may never obtain approval for or commercialize any of them 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 or the EMA in the European Union 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.

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

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

Among policy makers and payors in the United States and elsewhere, there is significant interest in promoting changes in healthcare systems with the stated goals of containing healthcare costs, improving quality and/or expanding access. In the United States, the pharmaceutical industry has been a particular focus of these efforts and has been significantly affected by major legislative initiatives. For example, in March 2010, the ACA was passed, which substantially changed the way healthcare is financed by both the government and private insurers, and significantly impacts the United States pharmaceutical industry. The ACA, among other things: (i) established an annual, nondeductible fee on any entity that manufactures or imports certain specified branded prescription drugs and biologic agents apportioned among these entities according to their market share in some government healthcare programs; (ii) expanded the entities eligible for discounts under the 340B drug pricing program; (iii) increased the statutory minimum rebates a manufacturer must pay under the Medicaid Drug Rebate Program to 23.1% and 13% of the average manufacturer price for most branded and generic drugs, respectively, and capped the total rebate amount for innovator drugs at 100% of the Average Manufacturer Price, or AMP; (iv) expanded the eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to additional individuals and by adding new eligibility categories for individuals with income at or below 133% (as calculated, it constitutes 138%) of the federal poverty level, thereby potentially increasing manufacturers' Medicaid rebate liability; (v) addressed a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for certain drugs and biologics that are inhaled, infused, instilled, implanted or injected; (vi) introduced a new Medicare Part D coverage gap discount program in which manufacturers must now agree to offer 70% point-of-sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period as a condition for the manufacturer's outpatient drugs to be covered under Medicare Part D (increased from 50%, effective January 1, 2019, pursuant to the Bipartisan Budget Act of 2018); (vii) 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 (viii) established the Center for Medicare and Medicaid Innovation at CMS to test innovative payment and service delivery models to lower Medicare and Medicaid spending, potentially including prescription drug.

There have been executive, judicial and Congressional challenges to certain aspects of the ACA. While Congress has not passed comprehensive repeal legislation, several bills affecting the implementation of certain taxes under the ACA have been signed into law. The Tax Cuts and Jobs Act of 2017, or Tax Act, included a provision that repealed, effective January 1, 2019, the tax-based shared responsibility payment imposed by the ACA on certain individuals who fail to maintain qualifying health coverage for all or part of a year that is commonly referred to as

the “individual mandate.” On June 17, 2021, the U.S. Supreme Court dismissed the most recent judicial challenge the ACA brought by several states without specifically ruling on the constitutionality of the ACA. Prior to the Supreme Court's decision, President Biden issued an executive order that initiated a special enrollment period 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, including among others, reexamining Medicaid demonstration projects and waiver programs that include work requirements, and policies that create unnecessary barriers to obtaining access to health insurance coverage through Medicaid or the ACA. It is possible that the ACA will be subject to judicial or congressional challenges in the future. It is unclear how such challenges and the healthcare reform measures of the Biden administration will impact the ACA or our business.

Other legislative changes have been proposed and adopted since the ACA was enacted. These changes include aggregate reductions to Medicare payments to providers of 2% per fiscal year pursuant to the Budget Control Act of 2011, which began in 2013, and due to subsequent legislative amendments to the statute, will remain in effect through 2031 unless additional Congressional action is taken. However, COVID-19 relief legislation suspended the 2% Medicare sequester from May 1, 2020 through March 31, 2022. Under current legislation the actual reduction in Medicare payments will vary from 1% in 2022 to up to 3% in the final fiscal year of this sequester. The American Taxpayer Relief Act of 2012, among other things, further reduced Medicare payments to several providers, including hospitals and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. Additionally, on March 11, 2021, President Biden signed the American Rescue Plan Act of 2021 into law, which eliminates the statutory Medicaid drug rebate cap, currently set at 100% of a drug’s average manufacturer price, for single source and innovator multiple source drugs, beginning January 1, 2024. These laws may result in additional reductions in Medicare, Medicaid and other healthcare funding, which could have an adverse effect on customers for our product candidates, if approved, and, accordingly, our financial operations.

Additionally, there has been heightened governmental scrutiny in the United States of America ("U.S") of pharmaceutical pricing practices in light of the rising cost of prescription drugs and biologics. Such scrutiny has resulted in several recent congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to product pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for products. At the federal level, the Trump administration used several means to propose or implement drug pricing reform, including through federal budget proposals, executive orders and policy initiatives. For example, on July 24, 2020 and September 13, 2020, the Trump administration announced several executive orders related to prescription drug pricing that seek to implement several of the administration’s proposals. As a result, the FDA also released a final rule on September 24, 2020 providing guidance for states to build and submit importation plans for drugs from Canada. Further, on November 20, 2020, HHS finalized a regulation removing safe harbor protection for price reductions from pharmaceutical manufacturers to plan sponsors under Part D, either directly or through pharmacy benefit managers, unless the price reduction is required by law. The implementation of the rule has been delayed by the Biden administration from January 1, 2022 to January 1, 2023 in response to ongoing litigation. The rule also creates a new safe harbor for price reductions reflected at the point-of-sale, as well as a safe harbor for certain fixed fee arrangements between pharmacy benefit managers and manufacturers, the implementation of which have also been delayed until January 1, 2023. Further, in November 2020, CMS issued an interim final rule implementing the Most Favored Nation, or MFN, Model under which Medicare Part B reimbursement rates will be calculated for certain drugs and biologicals based on the lowest price drug manufacturers receive in Organization for Economic Cooperation and Development countries with a similar gross domestic product per capita. The MFN Model regulations mandate participation by identified Part B providers and will apply in all United States and territories for a seven-year period beginning January 1, 2021, and ending December 31, 2027. As a result of litigation challenging the MFN Model, on December 27,2021, CMS published a final rule that rescinded the Most Favored Nation model interim final rule. In July 2021, the Biden administration released an executive order, “Promoting Competition in the American Economy,” with multiple provisions aimed at prescription drugs. In response to Biden’s executive order, on September 9, 2021, HHS released a Comprehensive Plan for Addressing High Drug Prices that outlines principles for drug pricing reform and sets out a variety of potential legislative policies that Congress could pursue to advance these principles. No legislation or administrative actions have been finalized to implement these

principles. In addition, Congress is considering drug pricing as part of other reform initiatives. Similar reform measures are been considered and adopted at the state level as well.

We expect that these and other healthcare reform measures that may be adopted in the future may result in more rigorous coverage criteria and in additional downward pressure on the price that we receive for any approved drug. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private payors. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability, or commercialize our drugs. It is also possible that additional governmental action is taken in response to the COVID-19 pandemic

In addition, FDA regulations and guidance may be revised or reinterpreted by the FDA in ways that may significantly affect our business and our products. For example, the results of the 2020 United States Presidential election may impact our business and industry. The Trump administration took several executive actions, including the issuance of a number of Executive Orders, that could impose significant burdens on, or otherwise materially delay, the FDA's ability to engage in routine oversight activities such as implementing statutes through rulemaking, issuance of guidance, and review and approval of marketing applications. It is difficult to predict whether or how these requirements will be interpreted and implemented, or whether they will be rescinded and replaced under the Biden administration. The policies and priorities of the new administration are unknown and could materially impact the regulations governing our product candidates. Any new regulations or guidance, or revisions or reinterpretations of existing regulations or guidance, may impose additional costs or lengthen FDA review times for ITIL-168, ITIL-306 or any future product candidates. We cannot determine how changes in regulations, statutes, policies, or interpretations when and if issued, enacted or adopted, may affect our business in the future. Such changes could, among other things, require:

- additional clinical trials to be conducted prior to obtaining approval;
- changes to manufacturing methods;
- recalls, replacements, or discontinuance of one or more of our products; and
- additional recordkeeping.

Such changes would likely require substantial time and impose significant costs, or could reduce the potential commercial value of ITIL-168, ITIL-306 or other product candidates, and could materially harm our business and our financial results. In addition, delays in receipt of or failure to receive regulatory clearances or approvals for any other products would harm our business, financial condition, and results of operations.

Risks Related to Employee Matters and Managing our Growth

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

We are highly dependent on the management, development, clinical, financial and business development expertise of our executive officers. Each of our executive officers may currently terminate their employment with us at any time. We do not maintain "key person" insurance for any of our executives or employees.

Recruiting and retaining qualified scientific and clinical personnel and, if we progress the development of our product pipeline toward scaling up for commercialization, manufacturing and sales and marketing personnel, will also be critical to our success. The loss of the services of our executive officers or other key employees could impede the achievement of our development and commercialization objectives and seriously harm our ability to successfully implement our business strategy. Furthermore, replacing executive officers and key employees may be difficult and may take an extended period of time because of the limited number of individuals in our industry with the breadth of skills and experience required to successfully develop, gain regulatory approval of and commercialize products. Competition to hire from this limited pool is intense, and we may be unable to hire, train, retain or motivate these key personnel on acceptable terms given the competition among numerous pharmaceutical and biotechnology companies for similar personnel. We also experience competition for the hiring of scientific and

clinical personnel from universities and research institutions. In addition, we rely on consultants and advisors, including scientific and clinical advisors, to assist us in formulating our development and commercialization strategy. Our consultants and advisors may be employed by employers 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 high quality personnel, our ability to pursue our growth strategy will be limited.

We expect to expand our clinical development and regulatory capabilities and potentially implement sales, marketing and distribution capabilities, and as a result, we may encounter difficulties in managing our growth, which could disrupt our operations.

As of December 31, 2021, we had 412 employees. As our development progresses, we expect to experience significant growth in the number of our employees and the scope of our operations, particularly in the areas of clinical product development, regulatory affairs, manufacturing and, if any of our product candidates receives marketing approval, sales, marketing and distribution. To manage our anticipated future growth, we must continue to implement and improve our managerial, operational and financial systems, expand our facilities and continue to recruit and train additional qualified personnel. Due to our limited financial resources and the limited experience of our management team in managing a company with such anticipated growth, we may not be able to effectively manage the expansion of our operations or recruit and train additional qualified personnel. The expansion of our operations may lead to significant costs and may divert our management and business development resources. Any inability to manage growth could delay the execution of our business plans or disrupt our operations.

Our employees, independent contractors, consultants, collaborators, principal investigators, CROs, suppliers and vendors may engage in misconduct or other improper activities, including non-compliance with regulatory standards and requirements.

We are exposed to the risk that our employees, independent contractors, consultants, collaborators, principal investigators, CROs, suppliers and vendors may engage in fraudulent conduct or other illegal activity. Misconduct by these parties could include intentional, reckless and/or negligent conduct that violates FDA regulations, including those laws requiring the reporting of true, complete and accurate information to the FDA, manufacturing standards, federal and state healthcare laws and regulations, and laws that require the true, complete and accurate reporting of financial information or data. In particular, sales, marketing and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to prevent fraud, 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. Misconduct by these parties could also involve the improper use of individually identifiable information, including, without limitation, information obtained in the course of clinical trials, which could result in regulatory sanctions and serious harm to our reputation. It is not always possible to identify and deter misconduct, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of significant civil, criminal and administrative penalties, including, without limitation, damages, fines, disgorgement, imprisonment, exclusion from participation in government healthcare programs, such as Medicare and Medicaid, additional reporting requirements and oversight if we become subject to a corporate integrity agreement or similar agreement to resolve allegations of non-compliance with these laws, and the curtailment or restructuring of our operations.

Risks Related to Ownership of our Common Stock and our Status as a Public Company

An active trading market for our common stock may not continue to be developed or sustained.

Prior to our initial public offering, there was no public market for our common stock. Although our common stock is listed on The Nasdaq Global Market, an active trading market for our shares may not continue to be developed or be sustained. If an active market for our common stock does not continue developing or is not sustained, it may be difficult for you to sell shares of our common stock at an attractive price or at all.

The trading price of the shares of our common stock may be volatile, and purchasers of our common stock could incur substantial losses.

Our stock price may be volatile. The stock market in general and the market for 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, investors may not be able to sell their common stock at or above the price paid for the shares. The market price for our common stock may be influenced by many factors, including:

- the commencement, enrollment or results of our clinical trials of ITIL-168, ITIL-306 or any future clinical trials we may conduct, or changes in the development status of our product candidates;
- any delay in our regulatory filings for ITIL-168, ITIL-306 or any other product candidate we may develop, and any adverse development or perceived adverse development with respect to the applicable regulatory authority's review of such filings, including without limitation the FDA's issuance of a "refusal to file" letter or a request for additional information;
- delays in or termination of clinical trials;
- adverse regulatory decisions, including failure to receive regulatory approval of our product candidates;
- unanticipated serious safety concerns related to the use of ITIL-168, ITIL-306 or any other product candidate;
- changes in financial estimates by us or by any equity research analysts who might cover our stock;
- conditions or trends in our industry;
- changes in the market valuations of similar companies;
- announcements by our competitors of new product candidates or technologies, or the results of clinical trials or regulatory decisions;
- stock market price and volume fluctuations of comparable companies and, in particular, those that operate in the biopharmaceutical industry;
- publication of research reports about us or our industry or positive or negative recommendations or withdrawal of research coverage by securities analysts;
- announcements by us or our competitors of significant acquisitions, strategic partnerships or divestitures;
- our relationships with our collaborators;
- announcements of investigations or regulatory scrutiny of our operations or lawsuits filed against us;
- investors' general perception of our company and our business;
- recruitment or departure of key personnel;
- overall performance of the equity markets;
- trading volume of our common stock;
- disputes or other developments relating to proprietary rights, including patents, litigation matters and our ability to obtain patent protection for our technologies;
- significant lawsuits, including patent or stockholder litigation;
- changes in the structure of healthcare payment systems;
- general political and economic conditions; and
- other events or factors, many of which are beyond our control.

The stock market in general, and the Nasdaq Global Select Market and biotechnology companies in particular, have experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of these companies, including very recently in connection with the ongoing COVID-19 pandemic, which has resulted in decreased stock prices for many companies notwithstanding the lack of a fundamental change in their underlying business models or prospects. Broad market and industry factors, including potentially worsening economic conditions and other adverse effects or developments relating to the ongoing COVID-19 pandemic, may negatively affect the market price of our common stock, regardless of our actual operating performance. The realization of any of the above risks or any of a broad range of other risks, including those described in this section, could have a significant and material adverse impact on the market price of our common stock.

In addition, in the past, stockholders have initiated class action lawsuits against pharmaceutical and biotechnology companies following periods of volatility in the market prices of these companies' stock. Such litigation, if instituted against us, could cause us to incur substantial costs and divert management's attention and resources from our business.

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

The trading market for our common stock will be influenced by the research and reports that equity research analysts publish about us and our business. As a newly public company, we have only limited research coverage by equity research analysts. Equity research analysts may elect not to provide research coverage of our common stock, and such lack of research coverage may adversely affect the market price of our common stock. In the event we do have equity research analyst coverage, we will not have any control over the analysts or the content and opinions included in their reports. The price of our stock could decline if one or more equity research analysts downgrade our stock or issue other unfavorable commentary or research. If one or more equity research analysts ceases coverage of our company or fails to publish reports on us regularly, demand for our stock could decrease, which in turn could cause our stock price or trading volume to decline.

A significant portion of our total outstanding shares are restricted from immediate resale but may be sold into the market in the near future. This 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 could occur at any time. If our stockholders sell, or the market perceives that our stockholders intend to sell, substantial amounts of our common stock in the public market, the market price of our common stock could decline significantly.

As of March 3, 2022, we had outstanding 129,129,995 shares of common stock.

In addition, we have filed a registration statement on Form S-8 under the Securities Act of 1933, as amended, or the Securities Act, registering the issuance of approximately 31.8 million shares of common stock subject to options or other equity awards issued or reserved for future issuance under our equity incentive plans. Shares registered under these registration statements on Form S-8 will be available for sale in the public market subject to vesting arrangements and exercise of options, the lock-up agreements described above and the restrictions of Rule 144 in the case of our affiliates.

Additionally, the holders of approximately 68.8 million shares of our common stock, or their transferees, have rights, subject to some conditions, to require us to file one or more registration statements covering their shares or to include their shares in registration statements that we may file for ourselves or other stockholders. If we were to register the resale of these shares, they could be freely sold in the public market. If these additional shares are sold, or if it is perceived that they will be sold, in the public market, the trading price of our common stock could decline.

Provisions in our corporate charter documents and under Delaware law may prevent or frustrate attempts by our stockholders to change our management and hinder efforts to acquire a controlling interest in us, and the market price of our common stock may be lower as a result.

There are provisions in our certificate of incorporation and bylaws that may make it difficult for a third party to acquire, or attempt to acquire, control of our company, even if a change of control was considered favorable by you and other stockholders. For example, our board of directors has the authority to issue up to 10,000,000 shares of preferred stock. The board of directors can fix the price, rights, preferences, privileges, and restrictions of the preferred stock without any further vote or action by our stockholders. The issuance of shares of preferred stock may delay or prevent a change of control transaction. As a result, the market price of our common stock and the voting and other rights of our stockholders may be adversely affected. An issuance of shares of preferred stock may result in the loss of voting control to other stockholders.

Our charter documents also contain other provisions that could have an anti-takeover effect, including:

- only one of our three classes of directors will be elected each year;
- stockholders will not be entitled to remove directors other than by a 66 2/3% vote and only for cause;
- stockholders will not be permitted to take actions by written consent;
- stockholders cannot call a special meeting of stockholders; and
- stockholders must give advance notice to nominate directors or submit proposals for consideration at stockholder meetings.

In addition, we are subject to the anti-takeover provisions of Section 203 of the Delaware General Corporation Law, which regulates corporate acquisitions by prohibiting Delaware corporations from engaging in specified business combinations with particular stockholders of those companies. These provisions could discourage potential acquisition proposals and could delay or prevent a change of control transaction. They could also have the effect of discouraging others from making tender offers for our common stock, including transactions that may be in your best interests. These provisions may also prevent changes in our management or limit the price that investors are willing to pay for our stock.

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

Our executive officers, directors and current beneficial owners of 5% or more of our common stock and their respective affiliates beneficially own a majority of our outstanding common stock. As a result, these persons, acting together, would be able to significantly influence all matters requiring stockholder approval, including the election and removal of directors, any merger, consolidation, sale of all or substantially all of our assets, or other significant corporate transactions.

Some of these persons or entities may have interests different than yours. For example, because many of these stockholders purchased their shares at prices substantially below the current market price of our common stock and have held their shares for a longer period, they may be more interested in selling our company to an acquirer than other investors, or they may want us to pursue strategies that deviate from the interests of other stockholders.

We are an "emerging growth company" and as a result of the reduced disclosure and governance requirements applicable to emerging growth companies, our common stock may be 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 we intend to take advantage of some of the exemptions from reporting requirements that are applicable to other public companies that are not emerging growth companies, including:

- not being required to comply with the auditor attestation requirements 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 in our periodic reports, proxy statements and registration statements; and
- not being required to hold a nonbinding advisory vote on executive compensation and stockholder approval of any golden parachute payments not previously approved.

We cannot predict if investors will find our common stock less attractive because we will rely on these exemptions. If some investors find our common stock less attractive as a result, there may be a less active trading market for our common stock and our stock price may be more volatile. We may take advantage of these reporting exemptions until we are no longer an emerging growth company. We will remain an emerging growth company until the earliest of (i) December 31, 2026, (ii) the last day of the fiscal year in which we have total annual gross revenue of at least $1.07 billion, (iii) the last day of the fiscal year in which we are deemed to be a "large accelerated filer" as defined in Rule 12b-2 under the Exchange Act, which would occur if (a) we have been reporting under the Exchange Act for at least twelve calendar months, (b) we have filed at least one Annual Report on Form 10-K and (c) the market value of our common stock held by non-affiliates exceeded $700.0 million as of the last business day of the second fiscal quarter of such year or (iv) the date on which we have issued more than $1.0 billion in non-convertible debt securities during the prior three-year period.

We will have broad discretion in the use of our cash and cash equivalents, including the net proceeds from our initial public offering.

We have broad discretion over the use of our cash and cash equivalents, including the net proceeds from our recent initial public offering. You may not agree with our decisions, and our use of the proceeds may not yield any return on your investment. Our failure to apply our cash and cash equivalents effectively could compromise our ability to pursue our growth strategy and we might not be able to yield a significant return, if any, on our investment of these net proceeds. You will not have the opportunity to influence our decisions on how to use our cash and cash equivalents.

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

You should not rely on an investment in our common stock to provide dividend income. We have not declared or paid cash dividends on our common stock to date. We currently intend to retain our future earnings, if any, to fund the development and growth of our business. As a result, capital appreciation, if any, of our common stock will be your sole source of gain for the foreseeable future. Investors seeking cash dividends should not purchase our common stock.

Our amended and restated certificate of incorporation provides that the Court of Chancery of the State of Delaware and the federal district courts of the United States of America will be the exclusive forums for substantially all disputes between us and our stockholders, which could limit our stockholders' ability to obtain a favorable judicial forum for disputes with us or our directors, officers or employees.

Our amended and restated certificate of incorporation provides that the Court of Chancery of the State of Delaware is the exclusive forum for the following types of actions or proceedings under Delaware statutory or common law:

- any derivative action or proceeding brought on our behalf;
- any action asserting a breach of fiduciary duty;
- any action asserting a claim against us arising under the Delaware General Corporation Law, our amended and restated certificate of incorporation, or our amended and restated bylaws; and

- any action asserting a claim against us that is governed by the internal-affairs doctrine.

This provision would not apply to suits brought to enforce a duty or liability created by the Exchange Act. Furthermore, Section 22 of the Securities Act creates concurrent jurisdiction for federal and state courts over all such Securities Act actions. Accordingly, both state and federal courts have jurisdiction to entertain such claims. To prevent having to litigate claims in multiple jurisdictions and the threat of inconsistent or contrary rulings by different courts, among other considerations, our amended and restated certificate of incorporation further provides that the federal district courts of the United States of America will be the exclusive forum for resolving any complaint asserting a cause of action arising under the Securities Act. While the Delaware courts have determined that such choice of forum provisions are facially valid, a stockholder may nevertheless seek to bring a claim in a venue other than those designated in the exclusive forum provisions. In such instance, we would expect to vigorously assert the validity and enforceability of the exclusive forum provisions of our amended and restated certificate of incorporation. This may require significant additional costs associated with resolving such action in other jurisdictions and there can be no assurance that the provisions will be enforced by a court in those other jurisdictions.

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

General Risk Factors

We have incurred and will continue to incur increased costs and demands upon management as a result of being a public company.

As a public company listed in the United States, we incur significant additional legal, accounting and other costs, which we anticipate could be between $1.0 million and $2.0 million annually. These additional costs could negatively affect our financial results. In addition, changing laws, regulations and standards relating to corporate governance and public disclosure, including regulations implemented by the SEC and the Nasdaq Stock Market, may increase legal and financial compliance costs and make some activities more time-consuming. These laws, regulations and standards are subject to varying interpretations and, as a result, their application in practice may evolve over time as new guidance is provided by regulatory and governing bodies.

We intend to invest resources to comply with evolving laws, regulations and standards, and this investment may result in increased general and administrative expenses and a diversion of management's time and attention from revenue-generating activities to compliance activities. If notwithstanding our efforts to comply with new laws, regulations and standards, we fail to comply, regulatory authorities may initiate legal proceedings against us and our business may be harmed.

Failure to comply with these rules might also make it more difficult for us to obtain some types of insurance, including director and officer liability insurance, and we might be forced to accept reduced policy limits and coverage or incur substantially higher costs to obtain the same or similar coverage. The impact of these events could also make it more difficult for us to attract and retain qualified persons to serve on our board of directors, on committees of our board of directors or as members of senior management.

If we fail to maintain proper and effective internal controls, our ability to produce accurate financial statements on a timely basis could be impaired.

We are subject to the reporting requirements of the Securities Exchange Act of 1934, the Sarbanes-Oxley Act of 2002, or the Sarbanes-Oxley Act, and the rules and regulations of the stock market on which our common stock is listed. The Sarbanes-Oxley Act requires, among other things, that we maintain effective disclosure controls and procedures and internal control over financial reporting.

As of our current fiscal year ending December 31, 2022, we must perform system and process evaluation and testing of our internal control over financial reporting to allow management to report on the effectiveness of our internal control over financial reporting in our Form 10-K filing for that year, as required by Section 404 of the Sarbanes-Oxley Act. This requires that we incur substantial additional professional fees and internal costs to expand our accounting and finance functions and that we expend significant management efforts. Prior to our initial public offering, we have never been required to test our internal control within a specified period, and, as a result, we may experience difficulty in meeting these reporting requirements in a timely manner.

We may identify weaknesses in our system of internal financial and accounting controls and procedures that could result in a material misstatement of our financial statements. Our internal control over financial reporting will not prevent or detect all errors and all fraud. A control system, no matter how well designed and operated, can provide only reasonable, not absolute, assurance that the control system's objectives will be met. Because of the inherent limitations in all control systems, no evaluation of controls can provide absolute assurance that misstatements due to error or fraud will not occur or that all control issues and instances of fraud will be detected.

If we are not able to comply with the requirements of Section 404 of the Sarbanes-Oxley Act in a timely manner, or if we are unable to maintain proper and effective internal controls, we may not be able to produce timely and accurate financial statements. If that were to happen, the market price of our stock could decline and we could be subject to sanctions or investigations by the stock exchange on which our common stock is listed, the Securities and Exchange Commission or other regulatory authorities.

Our effective tax rate may fluctuate, and we may incur obligations in tax jurisdictions in excess of accrued amounts.

We are subject to taxation in more than one tax jurisdiction. As a result, our effective tax rate is derived from a combination of applicable tax rates in the various places that we operate. In preparing our financial statements, we estimate the amount of tax that will become payable in each of such places. Nevertheless, our effective tax rate may be different than experienced in the past due to numerous factors, including passage of newly enacted tax legislation, changes in the mix of our profitability from jurisdiction to jurisdiction, the results of examinations and audits of our tax filings, our inability to secure or sustain acceptable agreements with tax authorities, changes in accounting for income taxes and changes in tax laws. Any of these factors could cause us to experience an effective tax rate significantly different from previous periods or our current expectations and may result in tax obligations in excess of amounts accrued in our financial statements.

We might not be able to utilize a significant portion of our net operating loss carryforwards.

We have generated and expect to continue to generate in the future significant federal and state net operating loss, or NOL, carryforwards. These NOL carryforwards could expire unused and be unavailable to offset future income tax liabilities. Under the Tax Cuts and Jobs, or the Tax Act, as modified by the CARES Act, federal NOLs incurred in taxable years beginning after December 31, 2017 and in future taxable years may be carried forward indefinitely, but the deductibility of such federal NOLs incurred in the taxable year beginning after December 31, 2020 is limited. It is uncertain how various states will respond to the Tax Act and CARES Act. In addition, under Section 382 of the Internal Revenue Code of 1986, as amended, and corresponding provisions of state law, if a corporation undergoes an "ownership change," which is generally defined as a greater than 50% change, by value, in its equity ownership over a three-year period, the corporation's ability to use its pre-change NOL carryforwards and other pre-change tax attributes to offset its post-change income or taxes may be limited. Our initial public offering, together with private placements and other transactions that have occurred since our inception, may have triggered such an ownership change pursuant to Section 382. We have not yet completed a Section 382 analysis. We may experience ownership changes as a result of subsequent shifts in our stock ownership, some of which may be outside of our control. If an ownership change occurs and our ability to use our NOL carryforwards is materially limited, it would harm our future operating results by effectively increasing our future tax obligations. We have a full valuation allowance for deferred tax assets including NOLs.

Our business activities will be subject to the Foreign Corrupt Practices Act, or FCPA, and similar anti-bribery and anti-corruption laws.

As we expand our business activities outside of the United States, including our clinical trial efforts, we will be subject to the FCPA and similar anti-bribery or anti-corruption laws, regulations or rules of other countries in which we operate. The FCPA generally prohibits offering, promising, giving, or authorizing others to give anything of value, either directly or indirectly, to a non-United States government official in order to influence official action, or otherwise obtain or retain business. The FCPA also requires public companies to make and keep books and records that accurately and fairly reflect the transactions of the corporation and to devise and maintain an adequate system of internal accounting controls. Our business is heavily regulated and therefore involves significant interaction with public officials, including officials of non-United States governments. 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 will be subject to regulation under the FCPA. Recently the SEC and Department of Justice have increased their FCPA enforcement activities with respect to biotechnology and pharmaceutical companies. There is no certainty that all of our employees, agents, suppliers, manufacturers, contractors, or collaborators, or those of our affiliates, will comply with all applicable laws and regulations, particularly given the high level of complexity of these laws. Violations of these laws and regulations could result in fines, criminal sanctions against us, our officers, or our employees, the closing down of facilities, including those of our suppliers and manufacturers, requirements to obtain export licenses, cessation of business activities in sanctioned countries, implementation of compliance programs, and prohibitions on the conduct of our business. Any such violations could include prohibitions on our ability to offer our products in one or more countries as well as difficulties in manufacturing or continuing to develop our products, and could materially damage our reputation, our brand, our international expansion efforts, our ability to attract and retain employees, and our business, prospects, operating results, and financial condition.

Disruptions at the FDA, the SEC and other government agencies caused by funding shortages or global health concerns 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 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 agency have fluctuated in recent years as a result. In addition, government funding of 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 may also slow the time necessary for new drugs or biologics to be reviewed and/or approved by necessary government agencies, which would adversely affect our business. For example, over the last several years, including most recently from December 22, 2018 to January 25, 2019, the United States government has shut down several times and certain regulatory agencies, such as the FDA and the SEC, have had to furlough critical FDA, SEC and other government employees and stop critical activities. If a prolonged government shutdown occurs, it could significantly impact the ability of the FDA to timely review and process our regulatory submissions, which could have a material adverse effect on our business.

Separately, in response to the COVID-19 pandemic, the FDA has periodically had to postpone inspections of foreign and domestic manufacturing facilities and products and has resumed such inspections subject to a risk-based prioritization system. Regulatory authorities outside the United States have adopted similar restrictions or other policy measures in response to the COVID-19 pandemic and may experience delays in their regulatory activities. If a prolonged government shutdown occurs, or if global health concerns continue to prevent the FDA or other regulatory authorities from conducting business as usual or conducting inspections, reviews or other regulatory activities, it could significantly impact the ability of the FDA to timely review and process our regulatory submissions, which could have a material adverse effect on our business.

Unfavorable global economic and political conditions could adversely affect our business, financial condition or results of operations.

Our results of operations could be adversely affected by general conditions in the global economy, the global financial markets and the global political conditions. Portions of our future clinical trials may be conducted outside of the United States and unfavorable economic conditions resulting in the weakening of the United States dollar would make those clinical trials more costly to operate. Furthermore, a severe or prolonged economic downturn, including a recession or depression resulting from the current COVID-19 pandemic or political disruption could result in a variety of risks to our business, including weakened demand for our product candidates or any future product candidates, if approved, and our ability to raise additional capital when needed on acceptable terms, if at all. A weak or declining economy or political disruption, including any international trade disputes, could also strain our manufacturers or suppliers, possibly resulting in supply disruption, or cause our customers to delay making payments for our potential products. Any of the foregoing could seriously harm our business, and we cannot anticipate all of the ways in which the political or economic climate and financial market conditions could seriously harm our business.

Item 1B. Unresolved Staff Comments.

None.

Item 2. Properties.

We control and operate our manufacturing site in Manchester, United Kingdom, which consists of 12,957 total square feet of leased laboratory and office space under eight leases that expire in July 2022, January 2023, and July 2024. We own and are developing our manufacturing facility in Tarzana, California, which has 102,607 square feet of clinical and manufacturing space, and lease 6,000 square feet of office space in Tarzana, California. Our Tarzana clinical manufacturing facility is expected to become operational in the first half of 2022.

Our headquarters is currently located in Dallas, Texas and consists of 5,055 square feet of leased office space under a lease that expires in April 2026. We also lease 42,240 square feet of laboratory and office space in Thousand Oaks, California, under a lease that expires in October 2026, and 7,036 square feet of leased laboratory and office space in Alderley Park, United Kingdom, under two leases that expire in November 2025 and April 2026, which in each case is subject to renewal. Additionally, we lease laboratory and office space in other parts of the United States. We believe that our facilities are adequate for our current needs, and that suitable additional alternative spaces will be available in the future on commercially reasonable terms.

Item 3. Legal Proceedings.

From time to time, we may become involved in legal proceedings arising in the ordinary course of our business. We are not currently subject to any material legal proceedings.

Item 4. Mine Safety Disclosures.

Not applicable.

Part II

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

Market Information for Common Stock

Our Class A common stock has been listed on the Nasdaq Global Select Market under the symbol "TIL" since March 19, 2021. Prior to that date, there was no public trading market for our common stock.

Holders of our Common Stock

As of March 3, 2022, there were 30 stockholders of record of our common stock. The actual number of stockholders is greater than this number of record holders and includes stockholders who are beneficial owners but whose shares are held in street name by brokers and other nominees.

Dividend Policy

We have never declared or paid, and do not anticipate declaring or paying in the foreseeable future, any cash dividends on our capital stock. We currently intend to retain all available funds and any future earnings to support our operations and finance the growth and development of our business.

Securities Authorized for Issuance under Equity Compensation Plans

See Item 12 of Part III of this Annual Report on Form 10-K regarding information about securities authorized for issuance under our equity compensation plans.

Recent Sales of Unregistered Equity Securities

On March 23, 2021, upon the closing of our initial public offering, all shares of our then-outstanding convertible preferred stock were automatically converted into 89,220,699 shares of common stock. The issuance of such shares of common stock was exempt from registration under Section 3(a)(9) of the Securities Act.

Use of Proceeds

On March 18, 2021, our Registration Statement on Form S-1, as amended (File No. 333-253620), was declared effective in connection with our initial public offering, pursuant to which we sold an aggregate of 18,400,000 shares of our common stock, including the full exercise of the underwriters' option to purchase additional shares, at a price to the public of $20.00 per share. Morgan Stanley & Co. LLC, Jefferies LLC, and Cowen and Company, LLC acted as joint book-running managers and Truist Securities, Inc. acted as lead manager for the offering.

The initial public offering closed on March 23, 2021. The aggregate net proceeds from our initial public offering, after underwriting discounts and commissions of $25.8 million and other offering expenses of $3.2 million, were $339.0 million. In connection with our initial public offering, no payments were made by us to directors, officers or persons owning ten percent or more of our common stock or to their associates or to our affiliates. There has been no material change in the planned use of proceeds from our initial public offering as described in our prospectus filed pursuant to Rule 424(b)(4) under the Securities Act with the SEC on March 22, 2021.

Issuer Purchases of Equity Securities

None.

Item 6. Reserved.

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

The following discussion and analysis should be read in conjunction with our financial statements and related notes included elsewhere in this Annual Report on Form 10-K. This discussion contains forward-looking statements that reflect our plans, estimates and beliefs and involve numerous risks and uncertainties, including but not limited to those described in the "Risk Factors" section of this Annual Report. Actual results may differ materially from those contained in any forward-looking statements. You should carefully read "Forward-Looking Statements" and "Risk Factors."

Forward-Looking Statements

The information in this discussion contains forward-looking statements and information within the meaning of Section 27A of the Securities Act of 1933, as amended, or the Securities Act, and Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act, which are subject to the "safe harbor" created by those sections. These forward-looking statements include, but are not limited to, statements concerning our strategy, future operations, future financial position, future revenues, projected costs, prospects and plans and objectives of management. The words "anticipates," "believes," "estimates," "expects," "intends," "may," "plans," "projects," "will," "would" and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. We may not actually achieve the plans, intentions, or expectations disclosed in our forward-looking statements and you should not place undue reliance on our forward-looking statements. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements that we make. These forward-looking statements involve risks and uncertainties that could cause our actual results to differ materially from those in the forward-looking statements, including, without limitation, the risks set forth in Part I, Item 1A, "Risk Factors" in this Annual Report on Form 10-K. The forward-looking statements are applicable only as of the date on which they are made, and we do not assume any obligation to update any forward-looking statements.

Overview

We are a clinical-stage biopharmaceutical company focused on developing an innovative cell therapy pipeline of autologous tumor infiltrating lymphocyte, or TIL, therapies for the treatment of patients with cancer. We have assembled an accomplished team with a successful track record in the development, manufacture, regulatory approval and commercialization of multiple cell therapies. Using our optimized and scalable manufacturing process, we are advancing our lead TIL product candidate, ITIL-168, for the treatment of advanced melanoma. Based on the clinical results from a compassionate use program with a TIL product that was manufactured using a prior version of the ITIL-168 manufacturing process, we submitted an investigational new drug application, or IND, to the U.S. Food and Drug Administration, or the FDA, and were authorized to initiate a Phase 2 trial in late 2021 with expected topline safety and efficacy data in 2023, which we believe could support a biologics license application, or BLA submission. We plan to initiate a Phase 1 trial of ITIL-168 in additional indications with unmet medical need, including cutaneous squamous cell carcinoma, non-small cell lung cancer, head and neck squamous cell carcinoma and cervical cancer, in 2022. ITIL-168 will be manufactured in our company-operated in-house manufacturing facilities for both our clinical trials and commercial sales, if approved.

We are also developing a novel class of genetically engineered TIL therapies using our Co-Stimulatory Antigen Receptor, or CoStAR, platform. These modified TILs still rely on their native, patient-specific T cell receptors, or TCRs, to bind to tumor neoantigens, but have been enhanced to express novel CoStAR molecules, which bind to shared tumor-associated antigens and provide potent costimulation to T cells within the tumor microenvironment. We believe that the ability of CoStAR to augment the activation of TILs upon native TCR-mediated recognition of tumor neoantigens has the potential to bring TIL therapy to patients with cancer types that have been historically resistant to immunotherapy. We anticipate filing an investigational new drug, or IND, application for our lead CoStAR-TIL product candidate, ITIL-306, in 2022.

We were founded in August 2018. In February 2019, we entered into a license agreement with Immetacyte Ltd., or Immetacyte, pursuant to which we obtained a worldwide license to Immetacyte's proprietary technology,

know-how and intellectual property for the research, development, manufacture and commercialization of TIL therapies. Immetacyte had been manufacturing a TIL product under a compassionate use program since 2011.

In March 2020, we acquired 100% of the share capital of Immetacyte for $0.8 million in cash consideration and 5.6 million shares of common stock valued at $0.58 per share. Pursuant to the purchase agreement, we are obligated to pay up to an aggregate of $14.8 million upon the achievement of certain clinical, regulatory and commercial sales milestones. In connection with the acquisition, we terminated the Immetacyte license agreement and associated payment obligations. The transaction was accounted for as a business combination and we recognized a $10.1 million intangible asset for the acquired in-process research and development, or IPR&D. We acquired Immetacyte primarily for this IPR&D, which is critical to achieve our objective of developing an innovative cell therapy pipeline of autologous TIL therapies for the treatment of patients with cancer, as well as the dedicated workforce of Immetacyte. Utilizing this IPR&D, we have optimized and scaled the manufacturing process and are advancing our lead TIL product candidate, ITIL-168, for the treatment of advanced melanoma. Based on the clinical results from a compassionate use program performed by Immetacyte at the Christie Hospital in Manchester, United Kingdom, with a TIL product that was manufactured using a prior version of the ITIL-168 manufacturing process, we initiated a Phase 2 trial.

Since inception, we have had significant operating losses. Our net loss was $156.8 million and $38 million for the years ended December 31, 2021 and 2020, respectively. As of December 31, 2021, we had an accumulated deficit of $201.7 million. As of December 31, 2021, we had cash, cash equivalents, restricted cash, and marketable securities of $454.6 million, which consists of $37.6 million in cash and cash equivalents, $0.5 million in restricted cash, and $416.5 million in marketable securities. We expect to continue to incur net losses for the foreseeable future, and we expect our research and development expenses, general and administrative expenses, and capital expenditures will continue to increase.

Recent Developments

In September 2021, following clearance from the U.S. Food and Drug Administration, or FDA, we initiated a global Phase 2 clinical trial of ITIL-168 in patients with advanced melanoma whose disease has relapsed after a PD-1 inhibitor and, if positive for a BRAF-activating mutation, a BRAF inhibitor. The Phase 2 trial was expanded during the IND review process, in consultation with FDA, to include additional populations of patients with advanced melanoma. Cohorts 2 and 3 will enroll patients who discontinued PD-1 inhibitor therapy due to intolerable toxicity and patients who had an unsatisfactory response to prior PD-1 inhibitor but have not yet experienced disease progression, respectively. On September 13, 2021, we reported clearance of our IND application by the FDA to initiate DELTA-1, a global Phase 2 clinical trial of ITIL-168 with registrational intent in patients with advanced melanoma. Topline safety and efficacy results are expected in 2023 and, if positive, we believe could support the submission of a BLA to the FDA.

Impact of the COVID-19 Pandemic on Our Operations

On March 11, 2020, the World Health Organization characterized the outbreak of COVID-19 as a global pandemic and recommended containment and mitigation measures. Since then, extraordinary actions have been taken by international, federal, state, and local public health and governmental authorities to contain and combat the outbreak and spread of COVID-19 in regions throughout the world, including the United Kingdom and California, where most of our operations are conducted. These actions include travel bans, quarantines, “stay-at-home” orders and similar mandates for many individuals to substantially restrict daily activities and for many businesses to curtail or cease normal operations. We have been carefully monitoring the COVID-19 pandemic as it continues to progress and its potential impact on our business. As a result of COVID-19, we have taken precautionary measures in order to minimize the risk of the virus to our employees. In addition, a significant portion of our workforce now works remotely. To date, we have been able to continue our key business activities and advance our clinical programs. However, in the future, it is possible that it will become more difficult to enroll participants in our clinical trials, which could delay our clinical development timelines. While the broader implications of the COVID-19 pandemic on our results of operations and overall financial performance remain uncertain, including any implications from the spread of the new Delta and Omicron variants of COVID-19, the COVID-19 pandemic has, to date, not had a

material adverse impact on our results of operations or our ability to raise funds to sustain operations. The economic effects of the pandemic and resulting societal changes are currently not predictable, and the future financial impacts could vary from those foreseen.

See “Risk Factors” for a further discussion of the potential adverse impact of COVID-19 on our business.

Components of Operating Results

Operating Expenses

Research and Development

Research and development expenses account for a significant portion of our operating expenses. Research and development expenses consist primarily of research and development, manufacturing, monitoring and other services payments and in-license payments to Immetacyte and, to a lesser extent, salaries, benefits, and other personnel-related costs, including stock-based compensation, professional service fees and facility and other related costs. In-licensing payments to Immetacyte were treated as IPR&D and expensed when incurred because the product candidates using the licensed TIL technology were determined to have no alternative future use. In addition, research and development expense is presented net of reimbursements from reimbursable tax and expenditure credits and grants from the U.K. government. For the years ended December 31, 2021 and 2020, we did not allocate our research and development expenses by program.

We expect our research and development expenses to increase substantially for the foreseeable future as we continue to ramp up our clinical development activities and incur expenses associated with hiring additional personnel to support our research and development efforts. Our expenditures on future nonclinical and clinical development programs are subject to numerous uncertainties in timing and cost to completion. The duration, costs and timing of clinical trials and development of product candidates will depend on a variety of factors, including:

- the scope, rate of progress and expenses of clinical trials and other research and development activities;
- potential safety monitoring and other studies requested by regulatory agencies;
- significant and changing government regulation; and
- the timing and receipt of regulatory approvals, if any.

The process of conducting the necessary clinical research to obtain FDA and other regulatory approval is costly and time consuming and the successful development of product candidates is highly uncertain. The risks and uncertainties associated with our research and development projects are discussed more fully in the section of this Annual Report titled “Risk Factors.” As a result of these risks and uncertainties, we are unable to determine with any degree of certainty the duration and completion costs of our research and development projects, or if, when or to what extent we will generate revenues from the commercialization and sale of any of our product candidates that obtain regulatory approval. We may never succeed in achieving regulatory approval for any of our product candidates.

General and Administrative

General and administrative expenses consist primarily of compensation and personnel-related expenses, including stock-based compensation, for our personnel in executive, finance and other administrative functions. General and administrative expenses also include professional fees paid for accounting, auditing, legal, tax and consulting services, insurance costs, recruiting costs, travel expenses, amortization and depreciation, and other general and administrative costs.

We expect our general and administrative expenses to increase substantially for the foreseeable future as we continue to increase our headcount to support our research and development activities and operations generally, the growth of our business and, if any of our product candidates receive marketing approval, commercialization

activities. We also expect to continue to incur additional expenses as a result of operating as a public company, including expenses related to compliance with the rules and regulations of the SEC, additional director and officer insurance expenses, investor relations activities and other administrative and professional services.

Other Income (Expense), Net

Other income (expense), net consists primarily of taxes, foreign exchange remeasurement gains and other expenses.

Income Tax Provision

We are subject to income taxes in the United States and the foreign jurisdiction where we operate, the United Kingdom. The United Kingdom has statutory tax rates that differ from those in the United States. Accordingly, our effective tax rates will vary depending on the relative proportion of United Kingdom to United States income, the availability of research and development tax credits, changes in the valuation of our deferred tax assets and liabilities and changes in tax laws.

In assessing the realizability of deferred tax assets, management considers whether it is more likely than not that some portion or all of the deferred tax assets will not be realized. The ultimate realization of deferred tax assets is dependent upon the generation of future taxable income during the periods in which those temporary differences become deductible. Due to the uncertainty of the business in which we operate, projections of future profitability are difficult and past profitability is not necessarily indicative of future profitability. At December 31, 2021, we maintained a full valuation allowance against net deferred tax assets for the U.S. entity. The valuation allowance has been provided based on the positive and negative evidence relative to our company, including the existence of cumulative net operating losses, or NOLs since the Company’s inception, and the inability to carryback these NOLs to prior periods. Furthermore, the Company determined that it is more likely than not that the benefit of these assets would not be realized in the foreseeable future. The timing and the reversal of the Company's valuation allowance will continue to be monitored. For United Kingdom purposes, the losses are being reported as a deferred tax asset to offset the net deferred tax liability by approximately $0.2 million.

Results of Operations

Comparison of the Years Ended December 31, 2021 and 2020

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

	Year Ended December 31,		Change
	2021	2020	$
Revenue	$ —	$ 138	$ (138)
Operating expenses:			
Research and development	107,251	19,399	87,852
General and administrative	48,309	14,383	33,926
Total operating expenses	155,560	33,782	121,778
Loss from operations	(155,560)	(33,644)	(121,916)
Other (expense), net	(1,195)	(3,943)	2,748
Loss before income tax expense	$ (156,755)	$ (37,587)	$ (119,168)
Income tax expense	(39)	(151)	112
Net loss	$ (156,794)	$ (37,738)	$ (119,056)

Research and Development Expenses

Research and development expenses were $107.3 million and $19.4 million for the years ended December 31, 2021 and 2020, respectively. The increase in research and development expenses during this period of $87.9 million was primarily due to:

- $54.1 million in costs from an increase in headcount and related costs for our research and development personnel, including increased stock-based compensation expense of $12.5 million, to support increased clinical trial activities, including clinical manufacturing;
- $18.7 million in costs related to research and clinical development activities, including from our clinical trials and expanded clinical manufacturing activities; and
- $15.0 million of expenses related to facilities and overhead, depreciation and amortization, and other expenses.

General and Administrative Expenses

General and administrative expenses were $48.3 million and $14.4 million for the years ended December 31, 2021 and 2020, respectively. The net increase of $33.9 million was primarily due to:

- $23.6 million in costs resulting from increased headcount and personnel related costs, including increased stock-based compensation expense of $12.0 million, to support our growing business and for preparation of clinical trials;
- $7.5 million in costs resulting from usage of consultants during the Company's initial public offering, mainly consisting of expenses for accounting consulting services of $1.6 million, executive and legal consultants of $2.8 million. Additionally, the increase was due to information technology consultants of $2.8 million in connection with our growing business; and

- $2.9 million in costs resulting from increased insurance expenses of $3.5 million offset by a decrease in facilities, office and administrative costs of $0.6 million.

Other (Expense), Net

Other expense, net was expense of $1.2 million and expense of $3.9 million for the years ended December 31, 2021 and 2020, respectively. The decrease of $2.7 million was due to a $4.4 million loss on the issuance of Series A preferred stock during the year ended December 31, 2020 offset by an increase gain on foreign currency transactions of $1.4 million, and an increase loss of $0.3 million in other expenses.

Income Tax Expense

Income tax expense, decreased from $0.2 million expense for the year ended December 31, 2020 to $39 thousand expense for the year ended December 31, 2021. During the year ended December 31, 2021, income tax expense mostly consisted of deferred foreign income taxes from our operations in the United Kingdom.

Liquidity and Capital Resources

Sources of Liquidity

Since our inception, we have not generated any revenue from product sales and we have incurred significant operating losses. We do not have any products that have achieved regulatory marketing approval and we do not expect to generate revenue from sales of any product candidates for several years, if ever.

As of December 31, 2021, we had cash, cash equivalents, restricted cash, and marketable securities of $454.6 million, which consists of $37.6 million in cash and cash equivalents, $0.5 million in restricted cash, and $416.5 million in marketable securities. Cash in excess of immediate requirements is invested in accordance with our investment policy, primarily with a view to liquidity and capital preservation.

In the first quarter of 2021, we raised aggregate net cash proceeds of $52.5 million from the issuance and sale of our Series C convertible preferred stock.

In March 2021, we raised net proceeds of $339.0 million in our IPO, pursuant to which we sold an aggregate of 18,400,000 shares of common stock.

Prior to our IPO, we funded our operations primarily through the issuance and sale of convertible preferred stock. From our inception through December 31, 2020, we raised net cash proceeds of $327.6 million from the issuance and sale of our convertible preferred stock. As of December 31, 2020, we had cash and cash equivalents of $241.7 million and an accumulated deficit of $44.9 million.

Future Funding Requirements

Based on our current operating plan, we believe our existing cash and cash equivalents, will be sufficient to fund our operating expenses and capital expenditure requirements into 2023. We have based this estimate on assumptions that may prove to be wrong, and we could utilize our available capital resources sooner than we expect. We expect to continue to expend significant resources for the foreseeable future.

We use our cash to fund operations, primarily to fund our research and development expenditures and related personnel costs. We expect our expenses to increase substantially for the foreseeable future as we continue to invest in research and development activities, particularly as we advance our product candidates into later stages of development and conduct larger clinical trials, seek regulatory approvals for and commercialize any product candidates that successfully complete clinical trials, hire additional personnel and invest in and grow our business, expand and protect our intellectual property portfolio, and operate as a public company. Because of the numerous

risks and uncertainties associated with research, development and commercialization of our product candidates, we are unable to estimate the exact timing and amount of our funding requirements. Our future operating expenditures will depend on many factors, including:

- the scope, rate of progress, costs and results of our clinical and preclinical development activities;
- the number and characteristics of any additional product candidates we develop or acquire;
- the timing of, and the costs involved in, obtaining regulatory approvals for ITIL-168, ITIL-306 or any future product candidates, and the number of trials required for regulatory approval;
- the cost of manufacturing ITIL-168, ITIL-306 or any future product candidates as well as any products we successfully commercialize;
- costs related to our manufacturing and other facilities;
- the cost of commercialization activities of our product candidates, if approved for sale, including marketing, sales and distribution costs;
- the timing, receipt and amount of sales of ITIL-168, ITIL-306 or any future product candidates, if approved;
- the costs associated with constructing our new clinical and commercial manufacturing facility and building out lab space;
- the extent to which we acquire or in-license other companies' product candidates and technologies;
- our ability to establish and maintain strategic collaborations, licensing or other arrangements and the financial terms of any such arrangements, including the timing and amount of any future milestone, royalty or other payments due under any such agreement;
- any product liability or other lawsuits;
- the expenses needed to attract, hire and retain skilled personnel;
- our investments in our operational, financial and management information systems;
- the costs associated with operating as a public company;
- the costs involved in preparing, filing, prosecuting, maintaining, defending and enforcing our intellectual property portfolio; and
- any delays or issues resulting from the ongoing COVID-19 pandemic.

In March 2020, we acquired 100% of the share capital of Immetacyte for total cash and non-cash consideration, including contingent consideration, of $15.4 million. In connection with the acquisition, we terminated the Immetacyte license agreement and associated payment obligations. The maximum consideration that remained unpaid at December 31, 2021, which payment is contingent on future events, was $14.5 million.

Until such time as we can generate significant revenue from sales of our product candidates, if ever, we expect to finance our operations through equity offerings, debt financings or other capital sources, which may include strategic collaborations or other arrangements with third parties. Additional funds may not be available to us on acceptable terms or at all. If we raise additional funds by issuing equity or convertible debt securities, our stockholders will suffer dilution and the terms of these securities may include liquidation or other preferences that adversely affect the rights of our common shareholders. Debt financing, if available, may involve restrictive covenants limiting our flexibility in conducting future business activities, and, in the event of insolvency, debt holders would be repaid before holders of our equity securities receive any distribution of our corporate assets. If we raise funds through collaborations or other similar arrangements with third parties, we may have to relinquish valuable rights to technologies, future revenue streams, product candidates or research programs or grant licenses on terms that may not be favorable to us and/or may reduce the value of our common shares. Our ability to raise additional funds may be adversely impacted by potential worsening global economic conditions and the recent disruptions to, and volatility in, the credit and financial markets in the United States and worldwide resulting from

the ongoing COVID-19 pandemic. If we fail to obtain necessary capital when needed on acceptable terms, or at all, it could force us to delay, limit, reduce or terminate our product development programs, commercialization efforts or other operations.

We lease various operating spaces in the United States and the United Kingdom under non-cancelable operating lease arrangements that expire on various dates through 2026. These arrangements require us to pay certain operating expenses, such as taxes, repairs, and insurance and contain landlord or tenant incentives or allowances, renewal and escalation clauses. As of December 31, 2021, our future minimum lease payments under non-cancelable lease agreements were $10.2 million, as discussed in Note 7 to the consolidated financial statements included elsewhere in this Annual Report on Form 10-K.

Our contractual obligations and commitments primarily consist of amounts we will pay to the general contractor constructing and developing land and buildings in Tarzana, California which we acquired in October 2020 for $37.6 million. We are in the process of developing this land for our United States operations and our contractual commitments for this development project are limited to unreimbursed spend by the general contractor. As of December 31, 2021, $63.2 million was contractually committed to the development of this project.

In the normal course of business, we enter into contracts with Clinical Research Organizations, or CROs, and other third parties for preclinical studies and clinical trials, research and development supplies and other testing and manufacturing services. We are contractually obligated for approximately $34.6 million in future services related to clinical trials, depending on whether certain milestones are met, as of December 31, 2021.

Cash Flows

The following table sets forth the significant sources and uses of cash for the periods set forth below (in thousands):

	Years Ended December 31,	
	2021	**2020**
Net cash provided by (used in):		
Cash used in operating activities	$ (122,138)	$ (29,616)
Cash used in investing activities	(474,396)	(51,122)
Cash provided by financing activities	393,164	313,048
Net (decrease) increase in cash, cash equivalents, and restricted cash	$ (203,370)	$ 232,310

Cash Flows from Operating Activities

Cash used in operating activities for the year ended December 31, 2021 was $122.1 million, which consisted of the net loss of $156.8 million partially offset by $30.3 million in non-cash charges and other adjustments to reconcile net loss to net cash used in operating activities and a $4.4 million net change to our net operating assets and liabilities. The non-cash charges primarily consisted of stock-based compensation of $26.2 million, and depreciation and amortization expense of $2.8 million. The net change in our operating assets and liabilities was primarily due to an increase of $3.9 million in accounts payable, an increase of $12.0 million in accrued expenses and other current liabilities, partially offset by an increase in $5.0 million in prepaid expenses and other current assets and an increase in $6.5 million in other long-term assets.

Cash used in operating activities for the year ended December 31, 2020 was $29.6 million, which consisted of the net loss of $37.7 million, partially offset by $6.6 million in non-cash charges and other adjustments to reconcile net loss to net cash used in operating activities and a $1.5 million net change to our net operating assets and liabilities. The non-cash charges primarily consisted of a loss on issuance of Series A convertible preferred stock of $4.4 million, loss on change in fair value of contingent consideration of $0.9 million, and stock-based compensation of $1.7 million. The net change in our operating assets and liabilities was primarily due to a decrease of $1.1 million in accounts payable, and an increase of $4.6 million in accrued expenses and other liabilities.

Cash Flows from Investing Activities

Cash used in investing activities for the year ended December 31, 2021 was $474.4 million, of which $57.8 million was related to purchases of property, plant and equipment, and $416.6 million was related to marketable securities.

Cash used in investing activities for the year ended December 31, 2020 was $51.1 million, which was related to purchases of property, plant and equipment of $50.8 million and $0.3 million related to the acquisition of Immetacyte.

Cash Flows from Financing Activities

Cash provided by financing activities for the year ended December 31, 2021 was $393.2 million, which was primarily related to net cash proceeds from our IPO of $339.0 million, net cash proceeds from the issuance of Series C convertible preferred stock of $52.5 million and cash proceeds from exercise of stock options of $1.8 million.

Cash provided by financing activities for the year ended December 31, 2020 was $313.0 million, which was primarily related to net cash proceeds from the issuance of Series A, Series B, and Series C convertible preferred stock of $312.6 million.

Contractual Obligations and Commitments

The Company's contractual obligations and commitments primarily consist of amounts we will pay to the general contractor constructing and developing our land and buildings in Tarzana, California. As of December 31, 2021, $63.2 million was contractually committed to the development of this project. Additionally, future minimum lease payments under noncancellable operating leases as of December 31, 2021 totaled $10.2 million, as discussed in Note 7 to the consolidated financial statements included elsewhere in this Annual Report on Form 10-K.

Critical Accounting Policies and Estimates

This management’s discussion and analysis of our financial condition and results of operations is based on our consolidated financial statements, which have been prepared in accordance with GAAP. The preparation of financial statements requires us to make estimates and assumptions that affect the reported amounts of assets and liabilities and the disclosure of contingent assets and liabilities at the date of the financial statements, as well as the reported expenses incurred during the reporting periods. Our estimates are based on our historical experience 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. Actual results may differ from these estimates under different assumptions or conditions.

While our significant accounting policies are described in the notes to our consolidated financial statements, we believe that the following critical accounting policies are most important to understanding and evaluating our reported financial results.

Stock-Based Compensation

We maintain a stock-based compensation plan as a long-term incentive for employees, directors and consultants. The plan allows for the issuance of stock options, stock appreciation rights and restricted stock units.

For stock-based awards with only service conditions, we recognize stock-based compensation expense for stock-based awards on a straight-line basis over the requisite service period and account for forfeitures as they occur. For stock-based awards with performance conditions, stock-based compensation expense is not recognized until the performance condition is probable to occur. Our stock-based compensation costs are based upon the grant date fair

value estimated using the Black-Scholes option pricing model. This model utilizes inputs that are highly subjective assumptions and generally require significant judgment. These assumptions include:

- Fair Value of Common Stock—Prior to our IPO in March 2021, the fair value of the shares of common stock underlying stock options had historically been determined by the board of directors. Because there has been no public market for the our common stock, the board of directors has determined fair value of the common stock at the time of grant of the option by considering a number of objective and subjective factors including important developments in our operations, contemporaneous valuations performed by an independent third party firm, sales of our convertible preferred stock, our operating results and financial performance, the conditions in the biotechnology industry and the economy in general, the stock price volatility of similar public companies and the lack of marketability of our common stock, among other factors. After our IPO in March 2021, the fair value of common stock is determined using the closing price of our common stock on the Nasdaq Global Select Market

- Expected Term — The expected term represents the period that stock-based awards are expected to be outstanding and is determined as the average of the time-to-vesting and the contractual life of the awards.

- Expected Volatility — Since we are privately held and do not have any trading history for our common stock, the expected volatility was estimated based on the average volatility for comparable publicly traded biotechnology companies over a period equal to the expected term of the stock option grants. The comparable companies were chosen based on their similar size, stage in the life cycle or area of specialty.

- Risk-Free Interest Rate — The risk-free interest rate is based on the U.S. Treasury zero coupon issues in effect at the time of grant for periods corresponding with the expected term of awards.

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

Acquisitions

We evaluate acquisitions of assets and related liabilities and other similar transactions to assess whether or not the transaction should be accounted for as a business combination or asset acquisition by first applying a screen to determine if substantially all of the fair value of the gross assets acquired is concentrated in a single identifiable asset or group of similar identifiable assets. If the screen is met, the transaction is accounted for as an asset acquisition. If the screen is not met, further determination is required as to whether or not we have acquired inputs and processes that have the ability to create outputs which would meet the requirements of a business.

Accounting for business combinations requires us to make significant estimates and assumptions, especially at the acquisition date with respect to intangible assets and contingent consideration liabilities. We use our best estimates and assumptions to accurately assign fair value to the intangible assets acquired at the acquisition date. Liabilities arising from the acquisition may include contingent consideration and require judgment in ascertaining the related fair value. Independent appraisals may be used to assist in the determination of these fair values. Such appraisals are based on significant estimates provided by us, such as projected revenues, earnings, cash flows, assembled workforce and schedule, with estimated probabilities of development milestone achievements utilized in determining the fair value of contract-related acquired intangible assets or contingent consideration. Adjustments to the fair value of contingent consideration are recorded in earnings. Additional information related to the acquisition date fair value of acquired net assets obtained during the allocation period, not to exceed one year, may result in changes to the recorded values of acquired assets and liabilities, resulting in an offsetting adjustment to the goodwill associated with the business acquired.

Recent Accounting Pronouncements

Information regarding recent accounting pronouncements applicable to us is included in Note 2 to the consolidated financial statements included elsewhere in this Annual Report on Form 10-K.

Emerging Growth Company and Smaller Reporting Company Status

We are an "emerging growth company" as defined in the JOBS Act. For so long as we remain an emerging growth company, we are permitted and intend to rely on certain exemptions from various public company reporting requirements, including not being required to have our internal control over financial reporting audited by our independent registered public accounting firm pursuant to Section 404 of the Sarbanes-Oxley Act of 2002, reduced disclosure obligations regarding executive compensation in our periodic reports and proxy statements and exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and any golden parachute payments not previously approved. Accordingly, the information contained herein may be different than the information you receive from other public companies in which you hold stock.

In addition, emerging growth companies can delay adopting new or revised accounting standards issued subsequent to the enactment of the JOBS Act until such time as those standards apply to private companies. We have elected to avail ourselves of this extended transition period for complying with new or revised accounting standards that have different effective dates for public and private companies until the earlier of the date that we (i) are no longer an emerging growth company or (ii) affirmatively and irrevocably opt out of the extended transition period provided in the JOBS Act. As a result, our financial statements may not be comparable to companies that comply with the new or revised accounting pronouncements as of public company effective dates.

We will remain an emerging growth company until the earliest of (i) December 31, 2026, (ii) the last day of the fiscal year in which we have total annual gross revenue of at least $1.07 billion, (iii) the last day of the fiscal year in which we are deemed to be a "large accelerated filer" as defined in Rule 12b-2 under the Exchange Act, which would occur if (a) we have been reporting under the Exchange Act for at least twelve calendar months, (b) we have filed at least one Annual Report on Form 10-K and (c) the market value of our common stock held by non-affiliates exceeded $700.0 million as of the last business day of the second fiscal quarter of such year or (iv) the date on which we have issued more than $1.0 billion in non-convertible debt securities during the prior three-year period.

In accordance with Section 12b-2 of the Exchange Act, we are no longer a smaller reporting company as of December 31, 2021. However, under Item 10(f)(2)(i) of Regulation S-K, we are permitted to avail ourselves of the scaled disclosure requirements available to smaller reporting companies in this Annual Report on Form 10-K. Having ceased to be a smaller reporting company, we will no longer be able to avail ourselves of such scaled disclosure beginning with our Quarterly Report on Form 10-Q for the quarterly period ending March 31, 2022.

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

Interest Rate Risk

We had cash, cash equivalents, restricted cash, and marketable securities of $454.6 million, which consists of $37.6 million in cash and cash equivalents, $0.5 million in restricted cash, and $416.5 million in marketable securities as of December 31, 2021. We generally hold our cash in interest-bearing money market accounts. We believe that historical fluctuations in interest rates have not had a material effect on our results of operations during the periods presented.

Due to the low risk profile of our marketable securities, a hypothetical ten percentage point change in interest rates during the period presented would not have had a material impact on our financial statements included elsewhere in this report.

The Company does not believe that inflation, or foreign currency exchange rate fluctuations have had a significant impact on its results of operations for any periods presented herein.

Item 8. Financial Statements and Supplementary Data.

INSTIL BIO, INC.

Index to financial statements

	Page
Report of Independent Registered Public Accounting Firm (PCAOB ID #34)	116
Consolidated Balance Sheets as of December 31, 2021 and 2020	117
Consolidated Statements of Operations and Comprehensive Loss for the Years ended December 31, 2021 and 2020	118
Consolidated Statements of Convertible Preferred Stock and Stockholders' Equity (Deficit) for the Years ended December 31, 2021 and 2020	119
Consolidated Statements of Cash Flow for the Years ended December 31, 2021 and 2020	120
Notes to the Consolidated Financial Statements	121

REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

To the stockholders and the Board of Directors of Instil Bio, Inc.:

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of Instil Bio, Inc. and subsidiaries (the "Company") as of December 31, 2021 and 2020, the related consolidated statements of operations and comprehensive loss, convertible preferred stock and stockholders' equity (deficit), 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 "financial statements"). In our opinion, the financial statements present fairly, in all material respects, the financial position of the Company as of December 31, 2021 and 2020, and the results of its operations and its cash flows for the each of the two years in the period ended December 31, 2021, in conformity with accounting principles generally accepted in the United States of America.

Basis for Opinion

These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on the Company's financial statements based on our audit. We are a public accounting firm registered with the Public Company Accounting Oversight Board (United States) (PCAOB) and are required to be independent with respect to the Company in accordance with the U.S. federal securities laws and the applicable rules and regulations of the Securities and Exchange Commission and the PCAOB.

We conducted our audits in accordance with the standards of the PCAOB. Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement, whether due to error or fraud. The Company is not required to have, nor were we engaged to perform, an audit of its internal control over financial reporting. As part of our audits, we are required to obtain an understanding of internal control over financial reporting but not for the purpose of expressing an opinion on the effectiveness of the Company's internal control over financial reporting. Accordingly, we express no such opinion.

Our audits included performing procedures to assess the risks of material misstatement of the financial statements, whether due to error or fraud, and performing procedures that respond to those risks. Such procedures included examining, on a test basis, evidence regarding the amounts and disclosures in the financial statements. Our audits also included evaluating the accounting principles used and significant estimates made by management, as well as evaluating the overall presentation of the financial statements. We believe that our audits provide a reasonable basis for our opinion.

/s/ Deloitte & Touche LLP

San Diego, California
March 7, 2022

We have served as the Company's auditor since 2020.

INSTIL BIO, INC.

CONSOLIDATED BALANCE SHEETS
(in thousands, except share and per share amounts)

	December 31,	
	2021	**2020**
ASSETS		
Current assets:		
Cash and cash equivalents	$ 37,590	$ 241,714
Marketable securities	416,509	—
Prepaid expenses and other current assets	9,921	4,424
Total current assets	464,020	246,138
Property, plant and equipment, net	121,999	55,341
Intangibles	10,104	10,104
Goodwill	5,722	5,722
Other long-term assets	8,138	1,707
Total assets	$ 609,983	$ 319,012
LIABILITIES, CONVERTIBLE PREFERRED STOCK AND STOCKHOLDERS' EQUITY (DEFICIT)		
Current liabilities:		
Accounts payable	$ 5,568	$ 3,495
Accrued expenses and other current liabilities	34,449	8,402
Contingent consideration, current portion	1,341	1,384
Total current liabilities	41,358	13,281
Contingent consideration, net of current portion	10,980	10,893
Deferred tax liabilities	2,426	2,471
Other long-term liabilities	20	—
Total liabilities	54,784	26,645
Commitments and contingencies (Note 7)		
Convertible preferred stock, par value $0.000001 per share; 10,000,000 and 74,350,598 shares authorized 0 and 70,176,046 shares issued and outstanding; $0 and $328,200 aggregate liquidation preference as of December 31, 2021, and 2020, respectively	—	331,966
Stockholders' equity (deficit):		
Common stock, par value $0.000001 per share; 300,000,000 and 111,000,000 shares authorized; 129,028,278 and 20,591,554 shares issued and outstanding as of December 31, 2021, and 2020, respectively	—	—
Additional paid-in capital	757,003	5,607
Accumulated other comprehensive loss	(87)	(283)
Accumulated deficit	(201,717)	(44,923)
Total stockholders' equity (deficit)	555,199	(39,599)
Total liabilities, convertible preferred stock and stockholders' equity (deficit)	$ 609,983	$ 319,012

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

INSTIL BIO, INC.

CONSOLIDATED STATEMENTS OF OPERATIONS AND COMPREHENSIVE LOSS
(in thousands, except share and per share amounts)

	Year Ended December 31,	
	2021	**2020**
Revenue	$ —	$ 138
Operating expenses:		
Research and development	107,251	19,399
General and administrative	48,309	14,383
Total operating expenses	155,560	33,782
Loss from operations	(155,560)	(33,644)
Other (expense), net	(1,195)	(3,943)
Loss before income tax expense	$ (156,755)	$ (37,587)
Income tax expense	(39)	(151)
Net loss	$ (156,794)	$ (37,738)
Other comprehensive income (loss):		
Foreign currency translation	246	(283)
Unrealized loss on available-for-sale securities, net	(50)	—
Net comprehensive loss	$ (156,598)	$ (38,021)
Net loss per share, basic and diluted	$ (1.48)	$ (2.36)
Weighted-average shares used in computing net loss per share, basic and diluted	105,993,230	15,997,794

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

INSTIL BIO, INC.

CONSOLIDATED STATEMENTS OF
CONVERTIBLE PREFERRED STOCK AND STOCKHOLDERS' EQUITY (DEFICIT)
(in thousands, except share and per share amounts)

	Convertible Preferred Stock		Common Stock		Additional Paid-in Capital	Accumulated Other Comprehensive Loss	Accumulated Deficit	Total Stockholders' Equity (Deficit)
	Shares	Amount	Shares	Amount				
Balance—December 31, 2019	15,000,000	$ 14,948	11,199,980	$ —	$ 293	$ —	$ (7,185)	$ (6,892)
Issuance of Series A convertible preferred shares at $1.00 per share, net of issuance costs of $34	10,000,000	14,366	—	—	—	—	—	—
Issuance of Series B convertible preferred shares at $4.92 per share, net of issuance costs of $357	34,600,523	169,843	—	—	—	—	—	—
Issuance of Series C convertible preferred shares at $12.58 per share, net of issuance costs of $191	10,575,523	132,809	—	—	—	—	—	—
Issuance of common stock in connection with an acquisition	—	—	5,640,000	—	3,243	—	—	3,243
Stock-based compensation	—	—	—	—	1,706	—	—	1,706
Exercise of stock options	—	—	3,751,574	—	365	—	—	365
Foreign currency translation	—	—	—	—	—	(283)	—	(283)
Net loss	—	—	—	—	—	—	(37,738)	(37,738)
Balance—December 31, 2020	70,176,046	$ 331,966	20,591,554	—	$ 5,607	$ (283)	$ (44,923)	$ (39,599)
Issuance of Series C convertible preferred shares at $12.58 per share	4,174,551	52,460	—	—	—	—	—	—
Issuance of common shares upon initial public offering net of underwriting discounts, commissions and offering costs	—	—	18,400,000	—	339,016	—	—	339,016
Conversion of redeemable convertible preferred stock	(74,350,597)	(384,426)	89,220,699	—	384,426	—	—	384,426
Issuance of common stock from exercises of stock options	—	—	816,025	—	1,757	—	—	1,757
Stock-based compensation	—	—	—	—	26,197	—	—	26,197
Net loss	—	—	—	—	—	—	(156,794)	(156,794)
Other comprehensive income	—	—	—	—	—	196	—	196
Balance—December 31, 2021	—	$ —	129,028,278	$ —	$ 757,003	$ (87)	$ (201,717)	$ 555,199

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

INSTIL BIO, INC.

CONSOLIDATED STATEMENTS OF CASH FLOWS
(in thousands)

	Year Ended December 31,	
	2021	**2020**
Cash flows from operating activities:		
Net loss	$ (156,794)	$ (37,738)
Adjustments to reconcile net loss to net cash used in operating activities:		
Loss on issuance of Series A convertible preferred stock	—	4,400
Stock-based compensation	26,197	1,706
Foreign exchange remeasurement loss (gain)	710	(643)
Change in fair value of contingent consideration	294	928
Depreciation and amortization	2,752	256
Other, net	342	—
Changes in operating assets and liabilities:		
Prepaid expenses and other current assets	(5,045)	(898)
Other long-term assets	(6,502)	(1,141)
Accounts payable	3,862	(1,054)
Accrued expenses and other current liabilities	12,046	4,568
Net cash used in operating activities	(122,138)	(29,616)
Cash flows from investing activities:		
Purchase of marketable securities	(1,107,565)	—
Maturities of marketable securities	691,000	—
Purchases of property, plant and equipment	(57,831)	(50,816)
Business acquisition, net of cash acquired	—	(306)
Net cash used in investing activities	(474,396)	(51,122)
Cash flows from financing activities:		
Proceeds from initial public offering, net of issuance costs	339,016	—
Proceeds from issuance of convertible preferred stock, net of issuance costs	52,460	312,618
Proceeds from exercise of stock options	1,757	365
Other financing activities	(69)	65
Net cash provided by financing activities	393,164	313,048
Net (decrease) increase in cash, cash equivalents, and restricted cash	(203,370)	232,310
Effect of exchange rate changes on cash, cash equivalents and restricted cash	(304)	559
Cash, cash equivalents and restricted cash—beginning of period	241,764	8,895
Cash, cash equivalents and restricted cash—end of period	$ 38,090	$ 241,764
Supplemental disclosure of noncash information:		
Conversion of preferred stock to common stock upon initial public offering	$ 384,426	$ —
Purchases of property, plant and equipment in accounts payable and accrued liabilities	$ 15,091	$ 2,922
Business acquisition through issuance of common stock and contingent consideration payable	$ —	$ 14,592
Deferred offering costs in accrued expenses and other current liabilities	$ —	$ 516

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

INSTIL BIO, INC.

Notes to Consolidated Financial Statements

1. Organization and Description of Business

Instil Bio Inc. (the “Company” or “Instil Bio”) is headquartered in Dallas, Texas and was incorporated in the state of Delaware in August 2018. The Company is a clinical-stage biopharmaceutical company focused on developing an innovative cell therapy pipeline of autologous tumor infiltrating lymphocyte (“TIL”) therapies for the treatment of patients with cancer. Principal operations commenced during the first quarter of 2019 when the Company in-licensed its foundational TIL technology.

2. Summary of Significant Accounting Policies

Basis of Presentation

The accompanying consolidated financial statements have been prepared in accordance with accounting principles generally accepted in the United States of America (“GAAP”) and include the accounts of the Company and its wholly owned subsidiaries Instil Bio (UK) Ltd. (formerly Immetacyte Ltd. (“Immetacyte”)) and Complex Therapeutics, LLC. Immetacyte was acquired on March 2, 2020 and Complex Therapeutics, LLC was incorporated on October 14, 2020. All intercompany balances and transactions have been eliminated in consolidation.

Use of Estimates

The preparation of the consolidated financial statements in conformity with GAAP requires management to make estimates and assumptions that affect the reported amounts of expenses during the reporting period. Significant estimates and assumptions made in the accompanying consolidated financial statements include but are not limited to the fair value of stock valuations prior to the Company's initial public offering, the fair value of acquired intangible assets, the fair value of contingent consideration payable, and the fair value of buildings and land in an asset acquisition. The Company evaluates its estimates and assumptions on an ongoing basis using historical experience and other factors and adjusts those estimates and assumptions when facts and circumstances dictate. Actual results could differ from those estimates.

Concentration of Credit Risk

Financial Instruments that potentially subject the Company to concentrations of credit risk consist primarily of cash and cash equivalents and marketable securities. The Company's cash and cash equivalents are held by two financial institutions in the United States ("U.S.") and one financial institution in the United Kingdom ("U.K."), which management believes to be financially sound, and accordingly, minimal credit risk exists with respect to the financial institutions. At times, the Company's deposits held in the U.S. and U.K. may exceed the Federal Depository Insurance Corporation and Financial Services Compensation Scheme, respectively, insured limits. During the years ended December 31, 2021 and 2020, the Company has not experienced any credit losses in such accounts or marketable securities.

Risks and Uncertainties

The Company is subject to a number of risks similar to other development-stage biopharmaceutical companies, including but not limited to, dependency on the clinical and commercial success of its product candidates, ability to obtain regulatory approval of its product candidates, uncertainty of broad adoption of its approved products, if any, by physicians and patients, manufacturing, the need to obtain adequate additional funding, significant competition, and protection of its intellectual property portfolio.

Stock Split and Initial Public Offering

On March 12, 2021, the Company effected a 1.2-for-1 stock split of the Company's common stock. The par value was not adjusted as a result of the stock split. The authorized shares as of March 12, 2021 were adjusted as a result of the stock split. All share and per share information included in the accompanying consolidated financial statements has been adjusted to reflect this stock split. The accompanying consolidated financial statements and notes thereto give retroactive effect to the stock split for all periods presented.

On March 23, 2021, the Company completed its initial public offering ("IPO") through an underwritten sale of an aggregate of 18,400,000 shares of its common stock at a price of $20.00 per share. The aggregate net proceeds from the offering, inclusive of an additional 2,400,000 common shares sold upon the full exercise of the underwriter's purchase option, after deducting underwriting discounts and commissions of $25.8 million and other offering expenses of $3.2 million, was $339.0 million.

Concurrent with the IPO, all then-outstanding shares of the Company's convertible preferred stock outstanding (see Note 8) were automatically converted into an aggregate of 89,220,699 shares of common stock and were reclassified into permanent equity. Further, immediately following the closing of the IPO, the Company amended and restated its certificate of incorporation such that the total number of shares of common stock authorized to be issued was 300,000,000 and the total number of shares of preferred stock authorized to be issued was 10,000,000. Following the IPO, there are no shares of convertible preferred stock outstanding.

COVID-19 Pandemic

On March 11, 2020, the World Health Organization characterized the outbreak of COVID-19 as a global pandemic and recommended containment and mitigation measures. Since then, extraordinary actions have been taken by international, federal, state, and local public health and governmental authorities to contain and combat the outbreak and spread of COVID-19 in regions throughout the world. These actions include travel bans, quarantines, "stay-at-home" orders and similar mandates for many individuals to substantially restrict daily activities and for many businesses to curtail or cease normal operations. As a result of COVID-19, the Company has taken precautionary measures in order to minimize the risk of the virus to its employees and the communities in which it operates. There has been minimal disruption in the Company's ability to ensure the effective operation of its business. While the broader implications of the COVID-19 pandemic on the Company's results of operations and overall financial performance remain uncertain, including any implications from the spread of the new Delta and Omicron variants of COVID-19, the COVID-19 pandemic has, to date, not had a material adverse impact on its results of operations or our ability to raise funds to sustain operations. The economic effects of the pandemic and resulting societal changes are currently not predictable, and the future financial impacts could vary from those foreseen.

Segments

Operating segments are identified as components of an enterprise about which separate discrete financial information is available for evaluation by the chief operating decision-maker in making decisions regarding resource allocation and assessing performance. The Company views its operations and manages its business in one operating segment.

Cash, Cash Equivalents, Restricted Cash and Marketable Securities

The Company considers all highly liquid investments purchased with original maturities of three months or less from the purchase date to be cash equivalents. Cash equivalents include amounts invested in money market accounts.

Restricted cash consists of a money market account which serves as collateral for the Company's employee corporate credit cards and is classified within other long-term assets on the consolidated balance sheets.

Our short-term marketable securities have original maturities of less than a year at date of purchase. We classify and account for our marketable securities as available-for-sale securities, which are carried at their fair

values based on the quoted market prices of the securities. Unrealized gains and losses are reported as accumulated other comprehensive income (loss). Realized gains and losses on available-for-sale securities are included in net loss in the period earned or incurred. As of December 31, 2021, marketable securities consisted of U.S. Treasury bills. The Company had no holdings of marketable securities as of December 31, 2020.

Short-term marketable securities are recorded at their estimated fair value. We periodically review whether our securities may be other-than-temporarily impaired, including whether or not (i) we have the intent to sell the security or (ii) it is more likely than not that we will be required to sell the security before its anticipated recovery. If one of these factors is met, we will record an impairment loss associated with our impaired investment. The impairment loss will be recorded as a write-down of investments in the consolidated balance sheets and a realized loss within other expense in the consolidated statements of operations. For the year ended December 31, 2021, there were no impairment losses for the investments.

The following table provides a reconciliation of cash, cash equivalents and restricted cash reported within the consolidated balance sheets that sum to the amounts shown in the consolidated statements of cash flows (in thousands):

	December 31,	
	2021	**2020**
Cash and cash equivalents	$ 37,590	$ 241,714
Restricted cash	500	50
Cash, cash equivalents and restricted cash	$ 38,090	$ 241,764

Fair Value Measurement

Assets and liabilities recorded at fair value on a recurring basis in the balance sheet are categorized based upon the level of judgment associated with the inputs used to measure their fair values. Fair value is defined as the exchange price that would be received for an asset or an exit price that would be paid to transfer a liability in the principal or most advantageous market for the asset or liability in an orderly transaction between market participants on the measurement date. Valuation techniques used to measure fair value maximize the use of observable inputs and minimize the use of unobservable inputs. The Company measures fair value based on a three-tier hierarchy, which prioritizes the inputs used in the valuation methodologies in measuring fair value as follows:

Level 1 —Observable inputs such as unadjusted, quoted prices in active markets for identical assets or liabilities at the measurement date.

Level 2 —Inputs (other than quoted prices included in Level 1) are either directly or indirectly observable for the assets or liabilities. These include quoted prices for similar assets or liabilities in active markets and quoted prices for identical or similar assets or liabilities in markets that are not active.

Level 3 —Unobservable inputs that are supported by little or no market activity and that are significant to the fair value of the assets or liabilities.

In determining fair value, the Company utilize quoted market prices, or valuation techniques that maximize the use of unobservable inputs to the extent possible as well as considers counterparty credit risk in its assessment of fair value.

Property, Plant and Equipment, Net

Property, plant and equipment, with the exception of land, is stated at cost less accumulated depreciation. Depreciation is computed on a straight-line basis over the estimated useful lives of the related assets. Maintenance and repairs are charged to operations as incurred. Upon sale or retirement of assets, the cost and related accumulated

depreciation are removed from the balance sheet and the resulting gain or loss is reflected in the consolidated statement of operations and comprehensive loss. The estimated useful lives of the Company's property, plant and equipment are as follows:

Laboratory equipment	7 years
Manufacturing equipment	7 years
Office and computer equipment	3 years
Leasehold improvements	Shorter of remaining lease term or estimated useful life

The Company owns land and buildings that it is in the process of developing for its U.S. operations. As described in Note 3, the buildings are still in development and depreciation will commence once the clinical manufacturing facility is ready for its intended use. A variety of costs are incurred in the development of a property. After determination is made to capitalize a cost, it is allocated to the specific component of a project that is benefited. Determination of when the development project is substantially complete and placed into service to begin depreciation involves a degree of judgment. The costs of land and buildings under development include specifically identifiable costs. The capitalized costs include pre-construction costs essential to the development of the property, development costs, and construction costs. When the development project is substantially complete and available for occupancy, the Company ceases capitalization of costs other than costs to improve the functionality or extend the useful lives of property, plant and equipment included as part of the project.

Impairment of Long-Lived Assets

The Company reviews its long-lived assets for impairment whenever events or changes in circumstances indicate that the carrying amount of an asset may not be recoverable or that the useful life is shorter than originally estimated. Recoverability of assets is measured by comparing the carrying amount of an asset to future undiscounted net cash flows expected to be generated by the asset over its remaining useful life. If such assets are impaired, the impairment recognized is measured by the amount by which the carrying amount of the assets exceeds the fair value of the assets. If the useful life is shorter than originally estimated, the Company depreciates or amortizes the remaining carrying value over the revised shorter useful life. Assets to be disposed of by sale are reflected at the lower of their carrying amount or fair value less cost to sell.

Business Combinations

The Company evaluates acquisitions of assets and related liabilities and other similar transactions to assess whether or not the transaction should be accounted for as a business combination or asset acquisition by first applying a screen to determine if substantially all of the fair value of the gross assets acquired is concentrated in a single identifiable asset or group of similar identifiable assets. If the screen is met, the transaction is accounted for as an asset acquisition. If the screen is not met, further determination is required as to whether or not the Company has acquired inputs and processes that have the ability to create outputs which would meet the requirements of a business.

The Company accounts for its business combinations using the acquisition method of accounting which requires recognition and measurement of all identifiable assets acquired and liabilities assumed at their full fair value as of the date it obtains control. The Company has determined the fair value of assets acquired and liabilities assumed based upon management's estimates of the fair values of assets acquired and liabilities assumed in the acquisitions. Goodwill represents the excess of the purchase price over the fair value of the net tangible and identifiable assets acquired. The Company accounts for contingent considerations at the acquisition-date fair value as part of the consideration transferred in the transactions.

While management has used its best estimates and assumptions to measure the fair value of the identifiable assets acquired and liabilities assumed at the acquisition date, these estimates are inherently uncertain and subject to refinement. As a result, during the measurement period, not to exceed one year from the date of acquisition, any changes in the estimated fair values of the net assets recorded for the acquisition will result in an adjustment to goodwill. Upon the conclusion of the measurement period of final determination of the values of assets acquired or

liabilities assumed, whichever comes first, the Company records any subsequent adjustments to the consolidated statements of operations and comprehensive loss. Acquisition-related costs, such as legal and consulting fees, are expensed as incurred.

The Company accounts for an asset acquisition by recognizing net assets based on the cost to the acquiring entity on a relative fair value basis, which includes transaction costs in addition to consideration given. Goodwill is not recognized in an asset acquisition; any excess consideration transferred over the fair value of the net assets acquired is allocated to the non-monetary identifiable assets and liabilities assumed based on relative fair values. Acquired in-process research and development ("IPR&D") is expensed as incurred provided there is no alternative future use.

Goodwill and other Indefinite Lived Intangible Assets

Indefinite-lived intangible assets consist of goodwill and IPR&D acquired in a business combination.

Goodwill represents the excess of the purchase price over the fair value of the net tangible and intangible assets acquired in a business combination. Goodwill is not amortized but is tested for impairment at least annually or more frequently if events or changes in circumstances indicate that the asset may be impaired. The Company's impairment tests are based on a single operating segment and reporting unit structure. If the carrying value of the reporting unit exceeds its fair value, an impairment charge is recognized for the excess of the carrying value of the reporting unit over its fair value.

IPR&D assets represent the fair value of incomplete research and development projects that had not reached technological feasibility as of the date of acquisition; initially, these are classified as IPR&D and are not subject to amortization. Once these research and development projects are completed, the asset balances are transferred from IPR&D to acquisition-related developed technology and are subject to amortization from this point forward. The Company reviews IPR&D for possible impairment annually or more frequently if events or changes in circumstances indicate that carrying amount may not be recoverable. Significant assumptions inherent in the evaluation and measurement of impairment include, but are not limited to, external factors such as industry and economic trends, and internal factors such as changes in the Company's business strategy and the Company's forecasts for specific projects.

Deferred Offering Costs

Costs directly related to the Company's IPO are deferred for expense recognition and instead capitalized and recorded within other long-term assets on the accompanying consolidated balance sheets. These costs consist of legal fees, accounting fees, and other applicable professional services. These deferred offering costs have been reclassified to additional paid in capital upon the closing of the IPO. There were no deferred offering costs capitalized as of December 31, 2021, as the IPO occurred in March 2021. As part of the IPO there were underwriting discounts and commissions of $25.8 million and other offering expenses of $3.2 million. As of December 31, 2020, $0.5 million of deferred offering costs were capitalized.

Revenue

Revenue recognized during the year ended December 31, 2020 is primarily related to the Company's commercial services agreement with a customer to provide storage and processing of clinical material harvested from patients related to the compassionate use program. The Company receives fixed fees per patient and procedure. Revenue related to this services agreement is recognized once services are performed as there is no alternative use for the asset once the activities is performed and the Company has the right to consideration in an amount that corresponds directly with the value provided to its customer and its performance completed to date. The commercial service agreement ended during 2020, therefore there was no revenue recognized during the year ended December 31, 2021.

Grant Proceeds

The Company receives government grants in the U.K. for the furtherance of certain research and development projects. Grant proceeds are recognized when all conditions of such grants are fulfilled or there is a reasonable assurance that they will be fulfilled. Grant proceeds are classified as a reduction of research and development expenses. For the years ended December 31, 2021 and 2020, $1.7 million and $1.2 million, of grant proceeds were recognized in research and development expenses on the Company's consolidated statements of operations and comprehensive loss, respectively.

Research and Development Expenses

Research and development ("R&D") costs are expensed as incurred. Advance payments for research and development activities are deferred as prepaid expenses, classified as current or noncurrent on the Company's consolidated balance sheets based on the estimated timing the related services will be performed and are expensed as the related services are performed. Costs incurred by third parties pursuant to contracts with research institutions and clinical research organizations are expensed as the contracted work is performed. The Company accrues for costs incurred as the services are being provided by monitoring the status of the trial or project and the invoices received from the external service providers. The Company adjusts its accrual as actual costs become known. If the actual timing of the performance of services or the level of effort varies significantly from the estimate, the Company will adjust the accrual accordingly. The Company has not experienced any material differences between accrued costs and actual costs incurred since its inception.

Research and development expenses are presented net of government grants, as described above, and R&D tax and expenditure credits from the U.K. government, which are recognized over the period necessary to match the reimbursement with the related costs when it is probable that the Company has complied with any conditions attached and will receive the reimbursement. Reimbursable R&D tax and expenditure credits were $1.8 million and $0.2 million in the years ended December 31, 2021 and 2020, respectively.

Stock-Based Compensation

The Company measures its stock-based awards granted to employees, non-employee directors, consultants and independent advisors based on the estimated grant date fair value of the awards. For stock-based awards with only service conditions, compensation expense is recognized over the requisite service period using the straight-line method. For stock-based awards that include performance conditions, compensation expense is not recognized until the performance condition is probable to occur. The Company uses the Black-Scholes option pricing model to estimate the fair value of its stock-based awards. The Black-Scholes option pricing model requires the Company to make assumptions and judgements about the variables used in the calculations, including the fair value of common stock, expected term, expected volatility of the Company's common stock, risk-free interest rate and expected dividend yield. The Company accounts for forfeitures of stock-based awards as they occur.

Income Taxes

Income taxes are accounted for using the asset and liability method. Deferred tax assets and liabilities are recognized for the future tax consequences attributable to differences between the financial statement carrying amounts or existing assets and liabilities and their respective tax bases. Deferred tax assets and liabilities are measured using the enacted tax rates expected to apply to taxable income in the years in which those temporary differences are expected to be recovered or settled. The effect on deferred tax assets and liabilities of a change in tax rates is recognized in income in the period of enactment. The Company records a valuation allowance to reduce deferred tax assets to an amount expected to be realized.

The Company recognizes the tax benefit from an uncertain tax position if it is more likely than not that the tax position will be sustained upon examination by the tax authorities, based on the merits of the position. The Company's policy is to recognize interest and penalties related to the underpayment of income taxes as a component

of income tax expense or benefit. To date, there have been no interest or penalties charged in relation to the unrecognized tax benefits.

Foreign Currency

The Company's reporting currency is the U.S. dollar. The functional currency of the Company's subsidiary located in the United Kingdom is the British Sterling. Balance sheets prepared in the functional currency are translated to the reporting currency at exchange rates in effect at the end of the accounting period, except for stockholders' deficit accounts, which are translated at rates in effect when these balances were originally recorded. Revenue and expense accounts are translated using an average exchange rate in effect during the period. The resulting foreign currency translation adjustments are recorded as a separate component of accumulated other comprehensive loss in the accompanying consolidated balance sheets.

Gains and losses resulting from exchange rate changes on intercompany transactions denominated in a currency other than the local currency are included in earnings as incurred as the related amounts are expected to be repaid in the foreseeable future.

Net Loss Per Share

Basic net loss per share is calculated by dividing the net loss by the weighted-average number of shares of the Company's common stock outstanding for the period, without consideration for potential dilutive shares of common stock. For purposes of the diluted net loss per share calculation, convertible preferred stock and common stock options are considered to be potentially dilutive securities. Diluted net loss per share is the same as basic net loss per share for each period presented since the effects of potentially dilutive securities are antidilutive given the net loss of the Company.

Comprehensive Loss

Comprehensive loss is defined as a change in equity during a period from transactions and other events and circumstances from non-owner sources. For the year ended December 31, 2021, comprehensive loss consists of foreign currency translation adjustments, and unrealized loss on available-for-sale securities net of tax. For the year ended December 31, 2020, comprehensive loss consists of foreign currency translation adjustments.

Emerging Growth Company Status

The Company is an emerging growth company, as defined in the Jumpstart Our Business Startups Act of 2012 (the "JOBS Act"). Under the JOBS Act, emerging growth companies can delay adopting new or revised accounting standards issued subsequent to the enactment of the JOBS Act until such time as those standards apply to private companies. The Company has elected to avail itself of this extended transition period for complying with new or revised accounting standards that have different effective dates for public and private companies until the earlier of the date that it (i) is no longer an emerging growth company or (ii) affirmatively and irrevocably opts out of the extended transition period provided in the JOBS Act. As a result, these consolidated financial statements may not be comparable to companies that comply with the new or revised accounting pronouncements as of public company effective dates.

Recent Accounting Pronouncements Not Yet Adopted

In February 2016, the FASB issued ASU No. 2016-02, Leases (Topic 842) which supersedes FASB ASC Topic 840, Leases (Topic 840) and provides principles for the recognition, measurement, presentation, and disclosure of leases for both lessees and lessors. The new standard requires the lessees to classify leases as either finance or operating leases based on the principle of whether or not the lease is effectively a financed purchase by the lessee, and such classification will determine whether lease expense is recognized based on an effective interest method or on a straight-line basis over the term of the lease, respectively. A lessee is also required to record a right-of-use asset and a lease liability for all leases with a term of greater than twelve months regardless of classification.

Leases with a term of twelve months or less will be accounted for similar to existing guidance for operating leases. In November 2019, the FASB issued ASU No. 2019-10, Financial Instruments—Credit Losses (Topic 326), Derivatives and Hedging (Topic 815), and Leases (Topic 842): Effective Dates, which revised the effective date for ASU No. 2016-02, Leases (Topic 842) for fiscal years beginning after December 15, 2020. In June 2020, the FASB issued ASU No. 2020-05, Revenue From Contracts With Customers (Topic 606) and Leases (Topic 842): Effective Dates for Certain Entities, further delaying the effective date for ASU No. 2016-02, Leases (Topic 842) to fiscal years beginning after December 15, 2021 and interim periods within fiscal years beginning after December 15, 2022. The Company immediately adopted ASU No. 2019-10 and ASU No. 2020-05 upon issuance by the FASB.

The new standard is effective for the Company on January 1, 2022. The Company will adopt the new standard effective January 1, 2022 using the modified retrospective transition approach. The Company has completed a substantial portion of its evaluation of the effect of adopting ASC 842 on its financial statements. Upon adoption on January 1, 2022, the Company expects to recognize estimated right-of-use assets and lease liabilities totaling approximately $15 million and $9 million, respectively, to reflect the present value of remaining lease payments under existing lease arrangements. The difference between the leased assets and lease liabilities represents the existing deferred rent liabilities balance, resulting from historical straight-lining of operating leases, which will be effectively reclassified upon adoption to reduce the measurement of the leased assets. The Company will apply the modified retrospective transition approach and will not recast prior periods. Although the Company is applying this approach, it does not expect to record a cumulative effect adjustment to the opening balance of retained earnings upon adoption. As permitted by the standard, the Company will elect the transition practical expedient package, which among other things, allows the carryforward of historical lease classifications. Accordingly, the Company will continue to apply Topic 840 prior to January 1, 2022, including Topic 840 disclosure requirements, in the comparative periods presented.

In June 2016, the FASB issued ASU No. 2016-13, Financial Instruments - Credit Losses (Topic 326): Measurement of Credit Losses on Financial Instruments. Additionally, the FASB issued ASU No. 2019-04, Codification Improvements to Topic 326, in April 2019 and ASU 2019-05, Financial Instruments — Credit Losses (Topic 326) — Targeted Transition Relief, in May 2019. The amendments affect loans, debt securities, trade receivables, net investments in leases, off-balance-sheet credit exposures, reinsurance receivables, and any other financial assets not excluded from the scope that have the contractual right to receive cash. In November 2019, the FASB issued ASU No. 2019-10, which defers the effective date of ASU No. 2016-13 for smaller reporting companies to fiscal years beginning after December 15, 2022, including interim periods within those fiscal years. The standard will be effective for the Company on January 1, 2022. The Company anticipates the adoption of the standard will not have a material impact on its consolidated financial statements.

In December 2019, the Financial Accounting Standards Board (FASB) issued Accounting Standards Update (ASU) No. 2019-12, Income Taxes (Topic 740): Simplifying the Accounting for Income Taxes. The standard simplifies the accounting for income taxes by removing certain exceptions to the general principles in Topic 740 and also improves consistent application by clarifying and amending existing guidance. The standard is effective for fiscal years beginning after December 15, 2021 and interim periods within fiscal years beginning after December 15, 2022. The Company anticipates the adoption of the standard will not have a material impact on its consolidated financial statements.

3. Balance Sheet Components

Property, Plant and Equipment, Net

Property, plant and equipment, net consist of the following (in thousands):

	December 31,	
	2021	**2020**
Land	$ 31,243	$ 31,243
Laboratory equipment	13,962	6,590
Buildings[(1)]	6,034	6,309
Office and computer equipment	2,239	1,510
Leasehold improvements	1,836	1,312
Manufacturing equipment	1,717	2,355
Vehicles	64	—
Construction work-in-progress	67,883	6,328
Total property, plant and equipment, gross	124,978	55,647
Less: accumulated depreciation	(2,979)	(306)
Total property, plant and equipment, net	$ 121,999	$ 55,341

(1) Relates to buildings acquired as described below which are being developed as part of the Company's clinical manufacturing facility in Tarzana, California. The buildings will be placed into service and depreciation will commence once the construction is complete and they are ready for intended use.

For the years ended December 31, 2021 and 2020 the Company recognized depreciation expense of $2.7 million and $0.3 million, respectively, in the consolidated statements of operations and comprehensive loss.

In October 2020, the Company acquired land and buildings in Tarzana, California, for $37.6 million. The Company is in the process of developing this land for its U.S. operations and has capitalized $67.0 million in work-in-progress costs associated with this development project. The Company's contractual commitments for this development project are limited to unreimbursed spend by the general contractor and as such, as of December 31, 2021 and 2020, $63.2 million and $6.3 million, respectively, is contractually committed to the development of this project. This acquisition is classified as an asset acquisition for which the Company records identifiable assets acquired at cost on a relative fair value basis. The most significant component of the allocation of fair value was to the Company's land and buildings.

Accrued Expenses and Other Current Liabilities

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

	December 31,	
	2021	**2020**
Accrued construction costs	$ 12,085	$ 302
Accrued compensation and benefits	11,928	3,983
Accrued operational expenses	5,292	1,589
Accrued research and development expenses	4,234	1,616
Current tax liabilities	524	631
Other current liabilities	386	281
Total accrued expenses and other current liabilities	$ 34,449	$ 8,402

4. Transactions with Immetacyte

License Agreement with Immetacyte

In February 2019, the Company entered into an Exclusive License & Research Services Agreement (the "License Agreement") with Immetacyte, whose key founders are also shareholders of the Company, pursuant to which the Company obtained a worldwide license to Immetacyte's proprietary technology, know-how and intellectual property for the research, development and manufacture of TIL therapies obtained from tumors using Immetacyte's technology.

The payments made for the license of the TIL technology were accounted for as IPR&D as part of an asset acquisition and were expensed as it was determined that there was no alternative future use for the license. The Company accounts for contingent consideration payable upon achievement of certain development or commercial milestones when the underlying contingency is resolved. For the year ended December 31, 2020, the Company recognized $0.6 million of IPR&D, which consisted of $0.3 million paid up front for the license and $0.3 million paid for achievement of a development milestone, which was recognized as a component of research and development expense in the Company's statement of operations and comprehensive loss.

Additionally, the Company was obligated to make payments for the research and development, manufacturing, monitoring and general services which included: (i) research and development services payments of $1.9 million annually for each of the first three years, (ii) manufacturing services payments of $1.2 million for the first annual period and $1.6 million for two years thereafter, and (iii) $0.3 million for monitoring and general services.

Upon the acquisition of Immetacyte, the License Agreement was terminated.

Acquisition of Immetacyte

In March 2020, the Company acquired 100% of the share capital of Immetacyte for $0.8 million in cash consideration, 5.6 million shares of common stock at an estimated fair value of $0.58 per share and up to an aggregate of $14.8 million of cash contingent consideration. The contingent consideration was additional cash consideration payable to the seller up until January 31, 2040 upon achievement of distinct product development milestones. The Company believes the acquisition, which includes the dedicated workforce of Immetacyte, will better position itself in developing an innovative cell therapy pipeline of autologous TIL therapies for the treatment of patients with cancer.

The fair value of consideration paid was as follows (in thousands):

Cash consideration	$	779
Common stock of 5,640,000 shares at an estimated fair value of $0.58 per share		3,243
Contingent consideration		11,349
Total consideration	$	15,371

The allocation of the purchase consideration was based on management's estimate of the acquisition date fair values of the assets acquired and liabilities assumed, as follows (in thousands):

Assets acquired:		
Net working capital	$	870
Property, plant and equipment		690
Intangibles		10,104
Total assets acquired		11,664
Goodwill		5,722
Deferred tax liabilities		(2,015)
Total purchase price	$	15,371

The acquisition was accounted for as a business combination and, accordingly, the total fair value of purchase consideration was allocated to the tangible and intangible assets acquired and liabilities assumed based on their fair values on the acquisition date. Due to the Company's pre-commercialization stage, many of the processes and methods used in the production of TILs were still in experimental development and pre-clinical stages and as such, resulted in a $10.1 million IPR&D asset. To value the IPR&D, the Company utilized the multi-period excess earnings method under the income approach. The method reflects the present value of the operating cash flows generated by this asset after taking into account the cost to realize the revenue, and an appropriate discount rate to reflect the time value and risk associated with the invested capital. These assumptions were applied to a relief-from-royalty model.

Within net working capital, was $0.8 million of acquired gross trade receivables, all of which has been collected. Goodwill is attributable to the assembled workforce and expected synergies from combining operations.

The goodwill recognized for this acquisition is not deductible for income tax purposes. From the acquisition date through December 31, 2021, there has been no change in the carrying amount of goodwill. Because the acquired IPR&D has an indefinite life, it is not amortized but rather evaluated for impairment. As of December 31, 2021 and 2020, IPR&D was not impaired.

The Company recognized acquisition-related costs of $0.9 million for the year ended December 31, 2020, which were expensed as incurred within general and administrative on the consolidated statements of operations and comprehensive loss.

5. Fair Value Measurement

The fair value of cash and cash equivalents approximates carrying value since cash and cash equivalents consist of short-term highly liquid investments with maturities of less than three months at the time of purchase. Cash and cash equivalents are quoted market prices in active markets for identical assets and are therefore classified as Level 1 assets. Money market funds are open-end mutual funds that invest in cash, government securities, and/or repurchase agreements that are collateralized fully. To the extent that these funds are valued based upon the reported net asset value, they are categorized in Level 1 of the fair value hierarchy.

Short-term marketable securities comprised of U.S. Treasury bills that are classified within Level 2 of the fair value hierarchy are valued based on other observable inputs, including broker or dealer quotations, alternative pricing sources or U.S. Government Treasury yield of appropriate term.

The following tables provide information by level for assets and liabilities that are measured at fair value on a recurring basis:

	As of December 31, 2021			
	Level 1	Level 2	Level 3	Total
	(In thousands)			
Financial Assets				
Money market funds	$ 18,493	$ —	$ —	$ 18,493
U.S. Treasury bills	—	416,509	—	416,509
Total	$ 18,493	$ 416,509	$ —	$ 435,002
Financial Liabilities				
Contingent consideration	$ —	—	12,321	$ 12,321

	As of December 31, 2020			
	Level 1	Level 2	Level 3	Total
	(In thousands)			
Financial Assets				
Money market funds	$ 106,138	—	—	$ 106,138
Financial Liabilities				
Contingent consideration	$ —	—	12,277	$ 12,277

There were no transfers in and out of Level 1, 2 and 3 measurements for the years ended December 31, 2021 and 2020. As of December 31, 2021 and 2020, there were no securities within Level 3 of the fair value hierarchy. The following table sets forth a summary of the changes in the fair value of the Company's Level 3 financial liabilities (in thousands):

	Year Ended December 31, 2021
Fair value, beginning balance	$ 12,277
Change in fair value	294
Development milestone achieved	(250)
Fair value, ending balance	$ 12,321

	Year Ended December 31, 2020
Fair value, beginning balance	$ —
Contingent consideration recorded as a result of Immetacyte acquisition	11,349
Change in present value of contingent consideration	928
Fair value, ending balance	$ 12,277

The Company’s acquisition of Immetacyte involved the potential for the payment of future contingent consideration upon the achievement of (i) certain product development milestones including, approval of studies and commencement and completion of certain product trials, or (ii) various other performance conditions including, receipt of final approval for the first marketing authorization and first commercial sale in certain geographical markets. Contingent consideration is recorded at the estimated fair value of the contingent payments on the acquisition date. The fair value of the contingent consideration is remeasured at the estimated fair value at each reporting period with the change in fair value recognized as income or expense within research and development expense in the consolidated statements of operations and comprehensive loss.

The Company determines the fair value of the contingent consideration by probability weighting scenarios of milestone achievements to determine the expected future contingent consideration payment, discounted to present value using an 8.5% discount rate based on the Company's pre-tax cost of debt on the acquisition date. The probability of payments ranged from 20% to 100% and the timing of future payments ranged from 2020 to 2026. In determining the likelihood of milestone achievements which trigger payouts related to the contingent consideration, the probabilities for various scenarios, as well as the discount rate used in the Company's calculations were based on internal unobservable projections. During the year ended December 31, 2020, no contingent consideration payments were made by the Company. As a result, as of December 31, 2020, the estimated future payments included the payment previously expected to be made in late 2020. As of December 31, 2020, the probability and timing of payments ranged from 20% to 100% and 2021 to 2026, respectively. As of December 31, 2020, the discount rate used in discounting the expected contingent consideration payments changed to 8% based on the Company's pre-tax cost of debt, which increased the fair value of the contingent consideration by $0.9 million from the acquisition date.

During the year ended December 31, 2021, the change of fair value related to the contingent consideration is due to the change in present value for the passage of time, as well as expected dates and probabilities of milestone achievement revisions. During the year ended December 31, 2021, the Company recognized a development milestone achievement, which is classified as an accrued expense in other current liabilities in the consolidated balance sheet as of December 31, 2021.

6. Financial Instruments

Marketable securities classified as available-for-sale at December 31, 2021 consisted of the following (in thousands):

	Maturity	Amortized Cost	Unrealized Gains	Unrealized Losses	Fair Value
U.S. Treasury bills	Less than one year	$ 416,559	$ —	$ (50)	$ 416,509

As of December 31, 2021, all marketable securities had original contractual maturities less than one year. There were no marketable securities classified as available-for-sale at December 31, 2020.

7. Commitments and Contingencies

Operating Leases

The Company leases various operating spaces in the U.S. and U.K. under non-cancelable operating lease arrangements that expire on various dates through the end of 2026. These arrangements require the Company to pay certain operating expenses, such as service charges, taxes, repairs, and insurance and contain landlord or tenant incentives or allowances, and renewal escalation clauses. The Company recognizes rent expense under these arrangements on a straight-line basis over the term of the lease and records the difference between the rent paid and recognition of rent expense as a deferred rent liability. Total rent expense was $3.0 million and $0.5 million for the years ended December 31, 2021 and 2020, respectively.

Future minimum lease payments under noncancellable operating leases as of December 31, 2021 were as follows (in thousands):

2022	$	2,411
2023		2,354
2024		2,215
2025		1,936
2026 and thereafter		1,272
Total	$	10,188

Construction Commitments

The Company's contractual commitments for the development of the Tarzana project are limited to unreimbursed spend by the general contractor and as such, as of December 31, 2021, was $63.2 million, which is contractually committed to the development of this project.

Legal Proceedings

From time to time, the Company may have certain contingent liabilities that arise in the ordinary course of its business activities. The Company accrues a liability for such matters when it is probable that future expenditures will be made and that such expenditures can be reasonably estimated. Significant judgment is required to determine both probability and the estimated amount. The Company does not expect that the resolution of these matters will have a material adverse effect on its financial position, results of operations or cash flows.

Indemnifications

The Company has entered into indemnification agreements with its directors and officers that may require the Company to indemnify its directors and officers against liabilities that may arise by reason of their status or service as directors or officers to the fullest extent permitted by Delaware corporate law. The Company currently has directors' and officers' insurance coverage that reduces its exposure and enables the Company to recover a portion of any future amounts paid. No liability associated with such indemnifications was recorded as of December 31, 2021 and 2020.

8. Equity

Common Stock

Each share of common stock has the right to one vote. The holders of common stock are also entitled to receive dividends whenever funds are legally available and if declared by the board of directors, subject to the prior rights of holders of all classes of stock outstanding having priority rights as to dividends. No cash dividends have been declared by the board of directors from inception.

In March 2020, the Company issued 5.6 million shares of its common stock at an estimated fair value of $0.58 per share to purchase Immetacyte (see Note 4).

In November 2020, the Company executed a limited recourse promissory note with its Chief Executive Officer ("CEO"), Bronson Crouch, in the amount of $1.1 million which was secured by a pledge of a total of 3.2 million shares of its common stock issued upon exercise of vested stock options. The note bore an interest rate of 2.5% per annum with a maturity date of the earlier of (i) five years from the date of the note or (ii) one business day prior to

the filing or submission of the Company's first registration statement covering the Company's common stock with the SEC. The principal and interest under the note may be repaid at any time without penalty. Because the Company only has partial recourse under the promissory note, the Company deemed the note receivable to be non-substantive. As such, the note receivable was not reflected in the consolidated financial statements and the related stock transaction will be recorded at the time the note receivable is settled in cash. As of December 31, 2020, the outstanding balance of the promissory note was $1.1 million. The promissory note was fully repaid in January 2021.

On March 23, 2021, the Company completed its IPO through an underwritten sale of an aggregate of an aggregate of 18,400,000 shares of its common stock at a price of $20.00 per share (see Note 2).

As of December 31, 2021, the Company had outstanding 129,028,278 shares of common stock.

Convertible Preferred Stock

As of December 31, 2020, there were 70,176,046 shares of preferred stock outstanding and the Company issued 4,174,551 shares of the Company Series C convertible preferred stock subsequent to December 31, 2020. Concurrent with the IPO, all then-outstanding shares of the Company's convertible preferred stock outstanding were automatically converted into an aggregate of 89,220,699 shares of common stock and were reclassified into permanent equity. Following the IPO, there are no shares of preferred stock outstanding.

Convertible preferred stock consisted of the following (in thousands, except shares):

	As of December 31, 2020		
	Shares Authorized	**Shares Issued and Outstanding**	**Aggregate Liquidation Preference**
Series A	25,000,000	25,000,000	$ 25,000
Series B	34,600,523	34,600,523	170,200
Series C	14,750,075	10,575,523	133,000
	74,350,598	70,176,046	$ 328,200

All outstanding shares of convertible preferred stock were converted on a 1.2-for-1 conversion ratio of shares of common stock on March 23, 2021, the date of closing of the Company's IPO (see Note 2).

The Company classified the convertible preferred stock outside of total stockholders' deficit because, in the event of certain deemed liquidation events that are not solely within the control of the Company, the shares would become redeemable at the option of the holders. The Company did not adjust the carrying values of the convertible preferred stock to the deemed liquidation values of such shares since a liquidation event was not probable of occurring at December 31, 2020. Subsequent adjustments to increase or decrease the carrying values to the ultimate liquidation values will be made only if, and when, it becomes probable that such a liquidation event will occur.

As of December 31, 2020, the holders of the Company's convertible preferred stock had various rights, preferences and privileges as follows:

Voting Rights

The holders of convertible preferred stock were entitled to cast the number of votes equal to the number of shares of common stock into which the shares of convertible preferred stock held by such holder were convertible as of the record date at any shareholder meeting of the Company. Except as provided by law or by the other provisions of the Company's amended and restated certificate of incorporation, holders of convertible preferred stock and

common stock were entitled to vote together as a single class. Holders of Series A convertible preferred stock, exclusively and as a separate class, were entitled to elect one member of the Company's board of directors and holders of Series B convertible preferred stock, exclusively and as a separate class, were entitled to elect three members to the Company's board of directors.

Dividends

Holders of convertible preferred stock were entitled to receive noncumulative cash dividends in an amount equal to 8% of their respective original (pre-split) issue price of $1.00, $4.92 and $12.58 for Series A, Series B and Series C convertible preferred stock, respectively, per annum per share (subject to appropriate adjustment in the event of any stock dividends, stock splits, stock combinations, recapitalizations or similar events), when and if declared by the Company's board of directors, prior and in preference to the holders of common stock. As of December 31, 2021, no dividends had been declared.

Liquidation

In the event of any voluntary or involuntary liquidation, dissolution or winding up of the Company or deemed liquidation event, the holders of shares of Series C convertible preferred stock were entitled to receive, prior and in preference to any distribution to the holders of Series B convertible preferred stock, an amount equal to the greater of (i) $12.58 per share, plus any dividends declared but unpaid or (ii) such amount per share as would have been payable in respect of each share of Series C convertible preferred stock had all shares of Series C convertible preferred stock been converted into common stock immediately prior to such liquidation, dissolution, winding up or deemed liquidation event. After the required payment to Series C convertible stockholders, holders of shares of Series B convertible preferred stock were entitled to receive, prior and in preference to any distribution to the holders of Series A convertible preferred stock, an amount equal to the greater of (i) $4.92 per share, plus any dividends declared but unpaid or (ii) such amount per share as would have been payable in respect of each share of Series B convertible preferred stock had all shares of Series B convertible preferred stock been converted into common stock immediately prior to such liquidation, dissolution, winding up or deemed liquidation event. After the required payment to Series B convertible stock holders, holders of shares of Series A convertible preferred stock were entitled to receive, prior and in preference to any distribution to the holders of common stock, an amount equal to the greater of (i) $1.00 per share, plus any dividends declared but unpaid or (ii) such amount per share as would have been payable in respect of each share of Series A convertible preferred stock had all shares of Series A convertible preferred stock been converted into common stock immediately prior to such liquidation, dissolution, winding up or deemed liquidation event. After the required payment is made to the preferred stockholders, the remaining assets of the Company, if any, were to be distributed to the holders of common stock pro rata based on the number of shares held by each such holder.

Optional Conversion Rights

Each share of convertible preferred stock was convertible, at the option of the holder, into such number of shares of common stock as was determined by dividing the original issue price for that series by the conversion price for such series in effect at the time of conversion. The conversion price was $0.83, $4.10 and $10.48 per share with respect to the shares of Series A, Series B and Series C convertible preferred stock, respectively, and was subject to certain anti-dilution adjustments.

Mandatory Conversion

Each share of convertible preferred stock was to be automatically converted into shares of common stock at the then effective conversion ratio for such share upon the earlier of (i) the closing of the sale of shares of common stock to the public at a price of at least $12.58 per share (subject to appropriate adjustment in the event of any stock dividend, stock split, combination or other similar recapitalization) with the gross cash proceeds to the Company of at least $100 million, or (ii) the date and time, or the occurrence of an event, specified by vote or written consent of the holders of at least a majority of outstanding shares of (a) Series B convertible preferred stock, (b) Series C

convertible preferred stock not also holding Series B convertible preferred stock, and (c) all convertible preferred stock.

2021 Preferred Stock Activity

All currently outstanding shares of convertible preferred stock were converted into an aggregate of 89,220,699 shares of common stock on March 23, 2021, the closing date of the Company's IPO (see Note 2). After the completion of the IPO, the Company's current amended and restated certificate of incorporation authorizes the Company to issue up to 10,000,000 shares of preferred stock at $0.000001 par value per share. The board of directors are authorized to provide for the issue of the shares of the preferred stock in one or more series, and to fix the number of shares and to determine or alter for each such series, such voting powers, full or limited, or no voting powers, and such designation, preferences, and relative, participating, optional, or other rights and such qualifications, limitations, or restrictions thereof, as shall be stated and expressed in subsequent resolution or resolutions adopted by the board providing for the issuance of such shares. As of December 31, 2021, there have been no shares of preferred stock issued and outstanding by the Company.

9. Stock-Based Compensation

2021 Equity Incentive Plan

In March 2021, the Company adopted the 2021 Equity Incentive Plan (the “2021 Plan”), which became effective in connection with the IPO. The 2021 Plan was approved by the Company’s board of directors and stockholders in March 2021. The 2021 Plan is an equity incentive plan pursuant to which the Company may grant the following awards: (i) incentive stock options; (ii) nonstatutory stock options; (iii) stock appreciation rights; (iv) restricted stock awards; (v) restricted stock unit awards; (vi) performance awards; and (vii) other forms of stock awards to employees, directors, and consultants, including employees and consultants of the Company’s affiliates. The 2021 Plan is a successor to the Company's 2018 Stock Incentive Plan (the “2018 Plan”). Following the effectiveness of the 2021 Plan, no further grants may be made under the 2018 Plan; however, any outstanding equity awards granted under the 2018 Plan will continue to be governed by the terms of the 2018 Plan.

The number of shares available for future issuance under the 2021 Plan is the sum of (1) 8,660,000 new shares of common stock, (2) 4,194,437 remaining shares of common stock reserved under the 2018 Plan that became available for issuance upon the effectiveness of the 2021 Plan and (3) the number of shares of common stock subject to outstanding awards under the 2018 Plan when the 2021 Plan became effective that thereafter expire or are forfeited, canceled, withheld to satisfy tax withholding or to purchase or exercise an award, repurchased by the Company or are otherwise terminated. The number of shares of common stock reserved for issuance under the 2021 Plan will automatically increase on January 1 of each year, for a period of ten years, from January 1, 2022 continuing through January 1, 2031, by 5% of the total number of shares of common stock outstanding on December 31 of the preceding calendar year, or a lesser number of shares as may be determined by the Company’s board of directors. Stock options granted by the Company to employees generally vest over four years with a one-year cliff.

As of December 31, 2021, 9,854,288 shares of common stock remained available for issuance under the 2021 Plan. As of December 31, 2021, the total number of shares authorized for issuance under the 2021 Plan was 12,854,437 shares.

The following summarizes option activity under the 2021 Plan:

	Shares Available for Grant	Shares Issuable Under Options	Weighted-Average Exercise Price	Weighted-Average Remaining Contract Term (in years)	Aggregate Intrinsic Value (in thousands)
Balance, December 31, 2019	3,892,000	6,508,000	$ 0.35	9.68	$ 1,106
Additional Shares Authorized	15,740,977				
Options granted[1]	(10,741,522)	10,741,522	$ 1.05		
Options forfeited	1,325,775	(1,325,775)	$ 0.71		
Options exercised[2]	—	(591,824)	$ 0.62		
Balance, December 31, 2020	10,217,230	15,331,923	$ 0.80	9.22	$ 78,857
Additional Shares Authorized	8,660,000				
Options granted[1]	(9,413,187)	9,413,187	$ 9.96		
Options forfeited	390,245	(390,245)	$ 5.28		
Options exercised	—	(3,976,028)	$ 0.44		
Balance, December 31, 2021	9,854,288	20,378,837	$ 5.17	8.75	$ 247,880
Exercisable, December 31, 2021		5,563,411	$ 1.94	8.32	$ 84,622
Vested and expected to vest, December 31, 2021		5,563,411	$ 1.94	8.32	$ 84,622

(1) Includes 2,519,137 and 1,101,600 stock options during the years ended December 31, 2021 and 2020, respectively, subject to only performance conditions.
(2) Excludes the exercise of 3,159,750 stock options that are subject to a limited recourse promissory note.

The aggregate intrinsic value disclosed in the above table is based on the difference between the exercise price of the stock option and the estimated fair value of the Company's common stock as of the respective period-end dates. There were 3,976,028 and 591,824 stock options exercised during the years ended December 31, 2021 and 2020, respectively. The aggregate intrinsic value of stock options exercised during the years ended December 31, 2021 and 2020, was $66.3 million and $1.5 million, respectively. The weighted-average grant date fair value of stock options granted during the years ended December 31, 2021 and 2020, was $11.59 and $0.68 per share, respectively.

The following table sets forth stock-based compensation included in the Company's statement of operations and comprehensive loss (in thousands):

	Year Ended December 31,	
	2021	2020
Research and development expense	$ 12,912	$ 418
General and administrative expense	13,285	1,288
Total stock-based compensation expense	$ 26,197	$ 1,706

As of December 31, 2021 and 2020, there was $69.5 million and $6.1 million of total unrecognized compensation cost related to unvested stock options granted under the 2018 Plan and 2021 Plan (excluding performance awards), which is expected to be recognized over a weighted average period of 2.24 years and 3.26 years, respectively.

The fair value of the Company's stock option awards was estimated at the date of grant using a Black-Scholes option pricing model with the following assumptions:

	Year Ended December 31,	
	2021	2020
Expected term (in years)	5.77 — 6.24	5.88 — 6.10
Expected volatility	72.52 % — 89.11%	82.54 % — 88.62%
Risk-free interest rate	0.51 % — 1.44%	0.31 % — 0.55%
Fair value of common stock	$5.95 — $26.44	$0.58 — $1.22
Expected dividend yield	—%	—%

Prior to the Company's IPO in March 2021, the fair value of the shares of common stock underlying stock options had historically been determined by the Company's board of directors. Because there has been no public market for the Company's common stock, the board of directors has determined fair value of the common stock at the time of grant of the option by considering a number of objective and subjective factors including important developments in the Company's operations, contemporaneous valuations performed by an independent third party firm, sales of the Company's convertible preferred stock, the Company's operating results and financial performance, the conditions in the biotechnology industry and the economy in general, the stock price volatility of similar public companies and the lack of marketability of the Company's common stock, among other factors. After the Company's IPO in March 2021, the fair value of common stock is determined using the closing price of the Company's common stock on the Nasdaq Global Select Market.

The Black-Scholes option pricing model requires the use of highly subjective assumptions which determine the fair value of stock-based awards. These assumptions include:

Expected term—The expected term represents the period that stock-based awards are expected to be outstanding and is determined as the average of the time-to-vesting and the contractual life of the awards.

Expected volatility—Since the Company is privately held and does not have any trading history for its common stock, the expected volatility was estimated based on the average volatility for comparable publicly traded biotechnology companies over a period equal to the expected term of the stock option grants. The comparable companies were chosen based on their similar size, stage in the life cycle or area of specialty.

Risk-free interest rate—The risk-free interest rate is based on the U.S. Treasury zero coupon issues in effect at the time of grant for periods corresponding with the expected term of awards.

Expected dividend yield—The Company has never paid dividends on its common stock and has no plans to pay dividends on its common stock. Therefore, the Company used an expected dividend yield of zero.

Performance Awards

During the years ended December 31, 2021 and 2020, 2,519,137 and 511,200 stock options vested to both employees and non-employees based upon performance conditions and strategic transactions. 2021 performance grants are expected to be recognized over a weighted average period of 2.92 years, and the 2020 performance grants have been vested. A strategic transaction has been defined as (a) a change in control, (b) the Company's next capital raise or (c) an initial public offering of the Company's shares, in which the Company receives at least $50.0 million in gross proceeds. Included in stock-based compensation expense for the year ended December 31, 2021 is $9.1 million related to awards where performance conditions were achieved. During the year ended December 31, 2020, the Company's Series B financing met the definition of a strategic transaction, triggering the immediate vesting of the performance awards. The Company recognized $0.8 million in compensation expense relating to the performance awards as of the closing of the Series B convertible preferred stock financing. As of December 31, 2021 and 2020, the Company had $21.1 million and $0.2 million of unrecognized compensation cost relating to these performance awards, calculated using the accelerated attribution method and the grant date fair value of the awards, respectively.

Employee Stock Purchase Plan

In March 2021, the Company adopted the Employee Stock Purchase Plan (the "ESPP"), which became effective in connection with the IPO. The ESPP was adopted by the Company's board of directors and stockholders in March 2021. The ESPP initially provides participating employees with the opportunity to purchase up to an aggregate of 1,237,000 shares of common stock. The number of shares of common stock reserved for issuance will automatically increase on January 1st of each calendar year for a period of up to ten years, commencing on January 1, 2022 and ending on (and including) January 1, 2031, in an amount equal to the lesser of (i) one percent (1%) of the total number of shares of capital stock outstanding on the last day of the calendar month before the date of the automatic increase, and (ii) 2,474,000 shares of common stock. Notwithstanding the foregoing, the board may act prior to the first day of any calendar year to provide that there will be no January 1st increase in the share reserve for such calendar year or that the increase in the share reserve for such calendar year will be a lesser number of shares of common stock than would otherwise occur pursuant to the preceding sentence.

10. Net Loss Per Share

The following outstanding potentially dilutive shares have been excluded from the calculation of diluted net loss per share for the periods presented due to their anti-dilutive effect:

	December 31,	
	2021	**2020**
Convertible preferred stock	—	70,176,046
Stock options to purchase common stock	20,378,837	9,012,423
Shares of common stock collateralizing note receivable from stockholder	—	3,159,750
Total	20,378,837	82,348,219

All outstanding shares of convertible preferred stock were converted on a 1.2-for-1 conversion ratio of shares of common stock on March 23, 2021, the date of the Company's IPO (see Note 2).

11. Income Taxes

The geographical breakdown of loss before provision for income taxes is as follows (in thousands):

	Year Ended December 31,	
	2021	**2020**
Domestic	$ (154,778)	$ (38,646)
Foreign	(1,977)	1,059
Loss before income taxes	$ (156,755)	$ (37,587)

The components of the provision for income taxes are as follows (in thousands):

	Year Ended December 31,	
	2021	2020
Current provision for income taxes:		
Foreign	$ —	$ (116)
Total current	—	(116)
Deferred tax provision:		
Domestic	18	—
Foreign	21	267
Total deferred	39	267
Total income tax expense	$ 39	$ 151

The following table presents a reconciliation of the Company's statutory federal income tax rate and effective tax rate:

	Year Ended December 31,	
	2021	2020
U.S federal taxes at statutory rate	21.0 %	21.0 %
Research and development tax credits	0.9 %	2.6 %
Stock-based compensation	(3.1)%	1.0 %
Permanent differences and other	(0.3)%	(1.3)%
Loss on issuance of Series A convertible preferred stock	0.0 %	(2.5)%
Statutory tax rate differences	2.7 %	0.1 %
Change in valuation allowance	(21.2)%	(21.3)%
Total	0.0 %	(0.4)%

The components of deferred tax liabilities consist of the following (in thousands):

	Year Ended December 31,	
	2021	2020
Deferred tax assets:		
Net operating loss carryforwards	$ 36,726	$ 8,120
Research and development credits	4,682	848
Accrued compensation and benefits	2,364	728
Stock-based compensation	744	142
Other temporary differences	1,033	29
Total gross deferred tax assets	45,549	9,867
Less: valuation allowance	(42,737)	(9,522)
Total deferred tax assets, net	2,812	345
Deferred tax liabilities:		
Intangible assets	(2,672)	(2,049)
Fixed assets	(2,566)	(641)
Other	—	(126)
Total gross deferred tax liabilities	(5,238)	(2,816)
Net deferred tax liabilities	$ (2,426)	$ (2,471)

The components of unrecognized tax benefits consist of the following (in thousands):

Balance at December 31, 2020:	$ —
Additions in 2021	2,339
Balance at December 31, 2021:	$ 2,339

In assessing the realizability of deferred tax assets, the Company considers whether it is more likely than not that some portion or all of the deferred tax assets will not be realized. The ultimate realization of deferred tax assets is dependent upon the generation of future taxable income during the periods in which those temporary differences become deductible. Due to the uncertainty of the business in which the Company operates, projections of future profitability are difficult and past profitability is not necessarily indicative of future profitability. The Company does not believe it is more likely than not that the deferred tax assets will be realized, and accordingly, the valuation allowance increased $33.2 million for the year ended December 31, 2021. As of December 31, 2021, the Company had net operating loss carryforwards for federal income tax purposes of $158.1 million, which will carryforward indefinitely, but may only offset 80% of the Company's taxable income. This change may require the Company to pay federal income taxes in future years despite generating a loss for federal income tax purposes in prior years. In addition, the Company has $14.2 million of net operating loss carryforwards available to reduce future taxable income, for California state income tax purposes for the year ended December 31, 2021. The state net operating loss carryforwards will begin to expire, if not utilized, in 2041.The Company has R&D credits of $4.1 million, and $3.7 million for federal and California, respectively, as of December 31, 2021. The federal R&D credits expire in 2040 and the California R&D credits carryforward indefinitely.

On March 27, 2020, the Coronavirus Aid, Relief, and Economic Security Act ("CARES Act") was enacted in response to the COVID-19 pandemic. The CARES Act, among other things, permits net operating loss carryforwards generated in taxable years beginning after December 31, 2017, to offset 100% of taxable income for taxable years beginning before January 1, 2021, and 80% of taxable income in taxable years beginning after

December 31, 2020. The CARES Act does not have a material impact on the Company's financial results for the year ended December 31, 2020.

The Company files income tax returns in the U.S. federal jurisdiction, various states where the Company has employees and/or significant business activities, and the U.K. As of December 31, 2021, the Company's federal and state returns through 2020 are still open to examination. The U.K. returns starting from 2016 are open to examination. The Company did not have any uncertain tax positions as of December 31, 2020. The Company had $2.3 million of uncertain tax positions as of December 31, 2021. The Company does not anticipate that the amount of existing unrecognized tax benefits will significantly increase or decrease during the next 12 months. The Company had no accrued interest or penalties related to uncertain tax positions as of December 31, 2021.

The Company has not completed a Section 382 study to assess whether an ownership change has occurred or whether there have been multiple ownership changes since the Company's formation. Pursuant to Internal Revenue Code Sections 382 and 383, annual use of the Company's net operating loss and research and development tax credit carryforwards may be limited in the event a cumulative change in ownership of more than 50% occurs within a three-year period. If eliminated, the related asset would be removed from the deferred tax asset schedule with a corresponding reduction in the valuation allowance. Due to the existence of the valuation allowance, limitations created by future ownership changes, if any, will not impact the Company's effective tax rate.

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

None

Item 9A. Controls and Procedures.

Evaluation of Disclosure Controls and Procedures

Our management, with the participation of our Chief Executive Officer and our Chief Financial Officer, has evaluated the effectiveness of our disclosure controls and procedures (as defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act of 1934, as amended, or the Exchange Act) as of the end of the period covered by this Annual Report. Based upon that evaluation, our Chief Executive Officer and Chief Financial Officer have concluded that, as of December 31, 2021, our disclosure controls and procedures were effective to provide reasonable assurance that information required to be disclosed by us in the reports that we file or submit under the Exchange Act is recorded, processed, summarized and reported, within the time periods specified in the SEC's rules and forms and to provide reasonable assurance that such information is accumulated and communicated to our management, including our Chief Executive Officer and Chief Financial Officer, as appropriate, to allow timely decisions regarding required disclosure.

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) that occurred during the period covered by this report that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting. We have not experienced any material impact on our internal control over financial reporting despite the fact that most of our employees are working remotely due to the COVID-19 pandemic. We are continually monitoring and assessing the COVID-19 situation on our internal controls to minimize the impact on their design and operating effectiveness.

Management's Report on Internal Control over Financial Reporting

The Annual Report on Form 10-K does not include a report of management's assessment regarding internal controls over financial reporting or an attestation report of our independent public accounting firm due to a transition period established by the rules of the SEC for newly public companies.

Inherent Limitations on Effectiveness of Controls

Our management, including our Chief Executive Officer and Chief Financial Officer, do not expect that our disclosure controls or our internal control over financial reporting will prevent all errors and all fraud. A control system, no matter how well conceived and operated, can provide only reasonable, not absolute, assurance that the objectives of the control system are met. Further, the design of a control system must reflect the fact that there are resource constraints, and the benefits of controls must be considered relative to their costs. Because of the inherent limitations in all control systems, no evaluation of controls can provide absolute assurance that all control issues and instances of fraud, if any, have been detected. These inherent limitations include the realities that judgments in decision-making can be faulty, and that breakdowns can occur because of a simple error or mistake. Additionally, controls can be circumvented by the individual acts of some persons, by collusion of two or more people or by management override of the controls. The design of any system of controls is also based in part upon certain assumptions about the likelihood of future events, and there can be no assurance that any design will succeed in achieving its stated goals under all potential future conditions, over time, controls may become inadequate because of changes in conditions, or the degree of compliance with policies or procedures may deteriorate. Because of the inherent limitations in a cost-effective control system, misstatements due to error or fraud may occur and not be detected.

Item 9B. Other Information.

None.

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

None.

Part III

Item 10. Directors, Executive Officers and Corporate Governance.

The information required by this Item and not set forth below will be set forth in the section headed "—Election of Directors" and "Information Regarding the Board of Directors and Corporate Governance" in our definitive Proxy Statement for our 2022 Annual Meeting of Stockholders to be filed with the SEC on or before April 30, 2022 (the "2022 *Proxy Statement*") and is incorporated in this report by reference.

We have adopted a code of ethics for directors, officers and employees, known as the Code of Business Conduct and Ethics. The Code of Business Conduct and Ethics is available on our website at http://www.instilbio.com under the Corporate Governance section of our Investors page. We will promptly disclose on our website (i) the nature of any amendment to the policy that applies to our principal executive officer, principal financial officer, principal accounting officer or controller, or persons performing similar functions and (ii) the nature of any waiver, including an implicit waiver, from a provision of the policy that is granted to one of these specified individuals, the name of such person who is granted the waiver and the date of the waiver.

Item 11. Executive Compensation.

The information required by this Item is incorporated by reference to the 2022 Proxy Statement.

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

The information required by this Item is incorporated by reference to the 2022 Proxy Statement.

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

The information required by this Item is incorporated by reference to the 2022 Proxy Statement.

Item 14. Principal Accountant Fees and Services.

The information required by this Item is incorporated by reference to the 2022 Proxy Statement.

Part IV

Item 15. Exhibits, Financial Statement Schedules.

(a) (1) Financial Statements.

The response to this portion of Item 15 is set forth under Part II, Item 8 above.

(a)(2) Financial Statement Schedules.

All schedules have been omitted because they are not required or because the required information is given in the Financial Statements or Notes thereto set forth under Item 8 above.

(a)(3) Exhibits.

The exhibits listed on the Exhibit Index are either filed or furnished with this report or incorporated herein by reference.

Exhibit Number	Description of Exhibit
3.1	Amended and Restated Certificate of Incorporation (incorporated herein by reference to Exhibit 3.1 to the Company's Current Report on Form 8-K (File No. 001-40215), filed with the SEC on March 23, 2021).
3.2	Amended and Restated Bylaws (incorporated herein by reference to Exhibit 3.2 to the Company's Current Report on Form 8-K (File No. 001-40215), filed with the SEC on March 23, 2021).
4.1*	Description of Securities
10.1†#	Share Purchase Agreement, by and between the Registrant and Immetacyte Limited, dated March 2, 2020 (incorporated herein by reference to Exhibit 10.1 to the Company's Registration Statement on Form S-1 (File No. 001-40215), filed with the SEC on February 26, 2021).
10.2+	2021 Equity Incentive Plan and Forms of Option Grant Notice and Agreement, Exercise Notice, Early Exercise Notice and Restricted Stock Award Notice (incorporated herein by reference to Exhibit 10.2 to the Company's Current Report on Form 8-K (File No. 001-40215), filed with the SEC on March 15, 2021).
10.3+	2018 Stock Incentive Plan and Forms of Stock Option Agreement, Notice of Stock Option Grant and Notice of Exercise and Common Stock Purchase Agreement (incorporated herein by reference to Exhibit 10.3 to the Company's Registration Statement on Form S-1 (File No. 001-40215), filed with the SEC on February 26, 2021).
10.4+	2021 Employee Stock Purchase Plan (incorporated herein by reference to Exhibit 10.4 to the Company's Current Report on Form 8-K (File No. 001-40215), filed with the SEC on March 15, 2021).
10.5+	Form of Indemnification Agreement with Executive Officers and Directors (incorporated herein by reference to Exhibit 10.5 to the Company's Current Report on Form 8-K (File No. 001-40215), filed with the SEC on March 15, 2021).
10.6+	Executive Employment Agreement, by and between the Registrant and Bronson Crouch, dated as of June 2020 (incorporated herein by reference to Exhibit 10.6 to the Company's Current Report on Form 8-K (File No. 001-40215), filed with the SEC on March 15, 2021).
10.7+	Executive Employment Agreement, by and between the Registrant and Zachary Roberts, M.D., Ph.D., dated as of June 2020 (incorporated herein by reference to Exhibit 10.7 to the Company's Current Report on Form 8-K (File No. 001-40215), filed with the SEC on March 15, 2021).

10.8+	Executive Employment Agreement, by and between the Registrant and Sandeep Laumas, M.D., dated as of June 2020 (incorporated herein by reference to Exhibit 10.8 to the Company's Current Report on Form 8-K (File No. 001-40215), filed with the SEC on March 15, 2021).
23.1*	Consent of Independent Registered Public Accounting Firm
24.1*	Power of Attorney (Included in signature pages hereto)
31.1*	Certification of Principal Executive Officer Pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
31.2*	Certification of Principal Financial Officer Pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934, as Adopted Pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
32.1*††	Certification of Principal Executive Officer Pursuant to 18 U.S.C. Section 1350, as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
32.2*††	Certification of Principal Financial Officer Pursuant to 18 U.S.C. Section 1350, as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.
101	The following financial information from Instil Bio Inc.'s Annual Report on Form 10-K for the year ended December 31, 2021 formatted in Inline XBRL (Extensible Business Reporting Language) includes: (i) the Consolidated Balance Sheets, (ii) the Consolidated Statements of Operations and Comprehensive Loss, (iii) the Consolidated Statements of Preferred Stock and of Stockholders Equity (Deficit), (v) the Consolidated Statements of Cash Flows, and (vi) Notes to the Consolidated Financial Statements.
104	Cover Page Interactive Data File (formatted as inline XBRL and contained in Exhibit 101)

---

* Filed herewith.
† Confidential treatment has been requested for portions of this agreement.
# Certain schedules to this agreement have been omitted in accordance with Item 601(b)(2) of Regulation S-K. A copy of any omitted schedules will be furnished supplementally to the SEC upon request.
\+ Indicates management contract or compensatory plan.
†† These certifications are being furnished solely to accompany this annual report on Form 10-K pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, and shall not be deemed "filed" by the registrant for purposes of Section 18 of the Securities Exchange Act of 1934, as amended, and are not to be incorporated by reference into any filing of the registrant, whether made before or after the date hereof, regardless of any general incorporation language in such filing.

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, the registrant has duly caused this report to be signed on its behalf by the undersigned thereunto duly authorized.

INSTIL BIO, INC.

March 7, 2022

By: /s/ Bronson Crouch

Bronson Crouch
Chief Executive Officer

Signatures And Power of Attorney

Know all persons by these presents, that each person whose signature appears below constitutes and appoints Bronson Crouch and Sandeep Laumas, M.D., jointly and each one of them, as his or her true and lawful attorneys-in-fact and agents, with full power of substitution and resubstitution, for him or her and in his or her name, place, and stead, in any and all capacities, to sign any and all amendments to this Annual Report on Form 10-K, and to file the same, with all exhibits thereto, and other documents in connection therewith, with the Securities and Exchange Commission, granting unto said attorneys-in-fact and agents full power and authority to do and perform each and every act and thing requisite and necessary to be done in and about the premises, as fully to all intents and purposes as he or she might or could do in person, hereby ratifying and confirming that all said attorneys-in-fact and agents, or his or her substitute or substitutes, may lawfully do or cause to be done by virtue hereof.

Pursuant to the requirements of the Securities Exchange Act of 1934, this Annual Report on Form 10-K has been signed below by the following persons on behalf of the Registrant and in the capacities and on the dates indicated:

Signature	Title	Date
/s/ Bronson Crouch Bronson Crouch	Chief Executive Officer and Chairman (Principal Executive Officer)	March 7, 2022
/s/ Sandeep Laumas, M.D. Sandeep Laumas, M.D.	Chief Financial Officer and Chief Business Officer (Principal Financial and Accounting Officer)	March 7, 2022
/s/ Gwendolyn Binder, Ph.D. Gwendolyn Binder, Ph.D.	Director	March 7, 2022
/s/ Neil Gibson, Ph.D. Neil Gibson, Ph.D.	Director	March 7, 2022
/s/ George Matcham, Ph.D. George Matcham, Ph.D.	Director	March 7, 2022
/s/ R. Kent McGaughy, Jr. R. Kent McGaughy, Jr.	Director	March 7, 2022
/s/ Jack Nielsen Jack Nielsen	Director	March 7, 2022

DESCRIPTION OF COMMON STOCK

The following description summarizes the most important terms of our common stock. Because it is only a summary, it does not contain all the information that may be important to you. For a complete description of the matters set forth in this "Description of Common Stock," you should refer to our amended and restated certificate of incorporation, as amended (the "certificate of incorporation"), and amended and restated bylaws (the "bylaws"), which are included as exhibits to our Annual Report on Form 10-K, and to the applicable provisions of Delaware law. Our authorized capital stock consists of 300,000,000 shares of common stock, $0.000001 par value per share and 10,000,000 shares of Convertible Preferred Stock, $0.000001 par value per share. Our board of directors is authorized, without stockholder approval, except as required by the listing standards of The Nasdaq Stock Market LLC, to issue additional shares of our capital stock. In addition, our board of directors may, without further action by our stockholders, designate the rights, preferences, privileges, and restrictions of our preferred stock in one or more series.

Voting Rights

Each holder of our common stock is entitled to one vote for each share on all matters submitted to a vote of the stockholders, including the election of directors. The affirmative vote of holders of at least 662/3% of the voting power of all of the then-outstanding shares of capital stock, voting as a single class, will be required to amend certain provisions of our certificate of incorporation, including provisions relating to amending our bylaws, the classified board, the size of our board, removal of directors, director liability, vacancies on our board, special meetings, stockholder notices, actions by written consent and exclusive forum.

Dividends

Subject to preferences that may be applicable to any then-outstanding preferred stock, holders of common stock are entitled to receive ratably those dividends, if any, as may be declared from time to time by the board of directors out of legally available funds.

Liquidation

In the event of our liquidation, dissolution or winding up, holders of common stock will be entitled to share ratably in the net assets legally available for distribution to stockholders after the payment of all of our debts and other liabilities and the satisfaction of any liquidation preference granted to the holders of any then-outstanding shares of preferred stock.

Rights and Preferences

Holders of common stock have no preemptive, conversion or subscription rights and there are no redemption or sinking fund provisions applicable to the common stock. The rights, preferences and privileges of the holders of common stock are subject to, and may be adversely affected by, the right of the holders of shares of any series of preferred stock that we may designate in the future.

Delaware Anti-Takeover Law and Provisions of Our Certificate of Incorporation and Bylaws

Our certificate of incorporation and our bylaws contain certain provisions that could have the effect of delaying, deterring or preventing another party from acquiring control of us, and therefore could adversely affect the market price of our common stock. These provisions and certain provisions of Delaware General Corporation Law (the "DGCL"), which are summarized below, may also discourage coercive takeover practices and inadequate takeover bids, and are designed, in part, to encourage persons seeking to acquire control of us to negotiate first with our board of directors. We believe that the benefits of increased protection of our potential ability to negotiate more favorable terms with an unfriendly or unsolicited acquirer outweigh the disadvantages of potentially discouraging a proposal to acquire us.

Delaware Anti-Takeover Law

We are subject to Section 203 of the DGCL ("Section 203"). Section 203 generally prohibits a public Delaware corporation from engaging in a "business combination" with an "interested stockholder" for a period of three years following the time that such stockholder became an interested stockholder, unless:

- prior to such time the board of directors of the corporation approved either the business combination or the transaction which resulted in the stockholder becoming an interested stockholder;
- upon consummation of the transaction which resulted in the stockholder becoming an interested stockholder, the interested stockholder owned at least 85% of the voting stock of the corporation outstanding at the time the transaction commenced, excluding for purposes of determining the voting stock outstanding (but not the outstanding voting stock owned by the interested stockholder) those shares owned (i) by persons who are directors and also officers and (ii) employee stock plans in which employee participants do not have the right to determine confidentially whether shares held subject to the plan will be tendered in a tender or exchange offer; or
- at or subsequent to such time the business combination is approved by the board of directors and authorized at an annual or special meeting of stockholders, and not by written consent, by the affirmative vote of at least 66 2/3% of the outstanding voting stock which is not owned by the interested stockholder.

Section 203 defines a business combination to include:

- any merger or consolidation involving the corporation and the interested stockholder;
- any sale, transfer, pledge or other disposition involving the interested stockholder of 10% or more of the assets of the corporation;
- subject to exceptions, any transaction that results in the issuance or transfer by the corporation of any stock of the corporation to the interested stockholder;
- subject to exceptions, any transaction involving the corporation that has the effect of increasing the proportionate share of the stock of any class or series of the corporation beneficially owned by the interested stockholder; and
- the receipt by the interested stockholder of the benefit of any loans, advances, guarantees, pledges or other financial benefits provided by or through the corporation.

In general, Section 203 defines an interested stockholder as any entity or person beneficially owning 15% or more of the outstanding voting stock of the corporation and any entity or person affiliated with or controlling or controlled by the entity or person.

Certificate of Incorporation and Bylaws

Our certificate of incorporation and bylaws contain certain provisions that are intended to enhance the likelihood of continuity and stability in the composition of the board of directors and which may have the effect of delaying, deferring or preventing a future takeover or change in control unless such takeover or change in control is approved by the board of directors. In addition, the authorization of undesignated preferred stock makes it possible for our board of directors to issue preferred stock with voting or other rights or preferences that could impede the success of any attempt to change our control. These provisions include:

Classified board of directors.

Our certificate of incorporation provides for our board of directors to be divided into three classes with staggered three-year terms. Only one class of directors will be elected at each annual meeting of our stockholders, with the other classes continuing for the remainder of their respective three-year terms. Because our stockholders do not have cumulative voting rights, stockholders holding a majority of the shares of common stock outstanding will be able to elect all of our directors. Our certificate of incorporation and our bylaws also provide that directors may be removed by the stockholders only for cause upon the vote of 66 2/3% or more of our outstanding common stock. Furthermore, the authorized number of directors may be changed only by resolution of the board of directors, and vacancies and newly created directorships on the board of directors may, except as otherwise required by law or determined by the board, only be filled by a majority vote of the directors then serving on the board, even though less than a quorum.

Under our certificate of incorporation and bylaws our stockholders do not have cumulative voting rights. Because of this, the holders of a majority of the shares of common stock entitled to vote in any election of directors can elect all of the directors standing for election, if they should so choose.

Action by Written Consent; Special Meetings of Stockholders.

Our certificate of incorporation and bylaws also provide that all stockholder actions must be effected at a duly called meeting of stockholders and eliminate the right of stockholders to act by written consent without a meeting. Our bylaws also provide that only our Chairman of the board, Chief Executive Officer or the board of directors pursuant to a resolution adopted by a majority of the total number of authorized directors may call a special meeting of stockholders.

Removal of Directors.

Our certificate of incorporation provides that our directors may be removed only for cause by the affirmative vote of at least 66 2/3% of the voting power of our outstanding shares of capital stock, voting together as a single class and entitled to vote in the election of directors. This requirement of a supermajority vote to remove directors could enable a minority of our stockholders to prevent a change in the composition of the board of directors.

Advance Notice Procedures.

Our bylaws also provide that stockholders seeking to present proposals before a meeting of stockholders to nominate candidates for election as directors at a meeting of stockholders must provide timely advance notice in writing, and specify requirements as to the form and content of a stockholder's notice.

Super Majority Approval Requirements.

The Delaware General Corporation Law generally provides that the affirmative vote of a majority of the shares entitled to vote on any matter is required to amend a corporation's certificate of incorporation or bylaws, unless either a corporation's certificate of incorporation or bylaws requires a greater percentage. Our certificate of incorporation and bylaws provide that the affirmative vote of holders of at least 66 2/3% of the outstanding shares of capital stock, voting together as a single class and entitled to vote in the election of directors are be required to amend, alter, change or repeal the bylaws and the certificate of incorporation. This requirement of a supermajority vote to approve amendments to our bylaws could enable a minority of our stockholders to exercise veto power over any such amendments.

Authorized but Unissued Shares.

Our authorized but unissued shares of common stock will be available for future issuance without stockholder approval. These additional shares may be utilized for a variety of corporate purposes, including future public offerings to raise additional capital, corporate acquisitions and employee benefit plans. The existence of authorized but unissued shares of common stock could render more difficult or discourage an attempt to obtain control of a majority of our common stock by means of a proxy contest, tender offer, merger or otherwise.

Exclusive Forum.

Our certificate of incorporation provides that the Court of Chancery of the state of Delaware will be the exclusive forum for the following types of actions or proceedings under Delaware statutory or common law:

- any derivative action or proceeding brought on our behalf;
- any action asserting a breach of fiduciary duty;
- any action asserting a claim against us arising pursuant to the Delaware General Corporation Law, our certificate of incorporation, or our bylaws; or
- any action asserting a claim against us that is governed by the internal affairs doctrine.

The provision would not apply to suits brought to enforce a duty or liability created by the Securities Exchange Act of 1934, as amended. Furthermore, Section 22 of the Securities Act of 1933, as amended, or the Securities Act, creates concurrent jurisdiction for federal and state courts over all such Securities Act actions. Accordingly, both state and federal courts have jurisdiction to entertain such claims. To prevent having to litigate claims in multiple jurisdictions and the threat of inconsistent or contrary rulings by different courts, among other considerations, our certificate of incorporation also provides that unless we consent in writing to the selection of an alternative forum, the federal district courts of the United States shall be the exclusive forum for the resolution of any complaint asserting a cause of action arising under the Securities Act.

While the Delaware courts have determined that such choice of forum provisions are facially valid, a stockholder may nevertheless seek to bring a claim in a venue other than those designated in the exclusive forum provisions. In such instance, we would expect to vigorously assert the validity and enforceability of the exclusive forum provisions of our certificate of incorporation. This may require significant additional costs associated with resolving such action in other jurisdictions and there can be no assurance that the provisions will be enforced by a court in those other jurisdictions

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

Our certificate of incorporation further provides that the federal district courts of the United States of America will be the exclusive forum for resolving any complaint asserting a cause of action arising under the Securities Act, subject to and contingent upon a final adjudication in the State of Delaware of the enforceability of such exclusive forum provision.

Transfer Agent and Registrar

The transfer agent and registrar for our common stock is American Stock Transfer & Trust Company, LLC. The transfer agent's address is 6201 15th Avenue, Brooklyn, New York 11219.

Listing

Our common stock is listed on the Nasdaq Global Select Market under the trading symbol "TIL."

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We consent to the incorporation by reference in Registration Statement No. 333- 255355 on Form S-8 of our report dated March 7, 2022, relating to the financial statements of Instil Bio, Inc. appearing in this Annual Report on Form 10-K for the year ended December 31, 2021.

/s/ DELOITTE & TOUCHE LLP

San Diego, California
March 7, 2022

EXHIBIT 31.1

CERTIFICATION OF PRINCIPAL EXECUTIVE OFFICER
PURSUANT TO EXCHANGE ACT RULE 13a-14(a)/15d-14(a)
AS ADOPTED PURSUANT TO SECTION 302
OF THE SARBANES-OXLEY ACT OF 2002

I, Bronson Crouch, certify that:

1. I have reviewed this Annual Report on Form 10-K of Instil Bio, 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(s) 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)) 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;

   (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 7, 2022

/s/ Bronson Crouch

Bronson Crouch

Chief Executive Officer (Principal Executive Officer)

EXHIBIT 31.2

CERTIFICATION OF PRINCIPAL FINANCIAL OFFICER
PURSUANT TO EXCHANGE ACT RULE 13a-14(a)/15d-14(a)
AS ADOPTED PURSUANT TO SECTION 302
OF THE SARBANES-OXLEY ACT OF 2002

I, Sandeep Laumas, certify that:

1. I have reviewed this Annual Report on Form 10-K of Instil Bio, 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(s) 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)) 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;

   (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 7, 2022

/s/ Sandeep Laumas

Sandeep Laumas

Chief Financial Officer (Principal Financial Officer)

Exhibit 32.1

CERTIFICATION OF CHIEF EXECUTIVE OFFICER
PURSUANT TO 18 U.S.C SECTION 1350,
AS ADOPTED PURSUANT TO
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

Pursuant to the requirement set forth in Rule 13a-14(b) of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), and Section 1350 of Chapter 63 of Title 18 of the United States Code (18 U.S.C. §1350), Bronson Crouch, Chief Executive Officer of Instil Bio, Inc. (the "Company"), hereby certifies that, to the best of his knowledge:

1. The Company's Annual Report on Form 10-K for the period ended December 31, 2021, to which this Certification is attached as Exhibit 32.1 (the "Annual Report") fully complies with the requirements of Section 13(a) or Section 15(d) of the Exchange Act, and

2. The information contained in the Annual Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

In Witness Whereof, the undersigned has set their hand hereto as of the March 7, 2022.

/s/ Bronson Crouch

Bronson Crouch

Chief Executive Officer

"This certification accompanies the Form 10-K to which it relates, is not deemed filed with the Securities and Exchange Commission and is not to be incorporated by reference into any filing of Instil Bio, Inc. under the Securities Act of 1933, as amended, or the Securities Exchange Act of 1934, as amended (whether made before or after the date of the Form 10-K), irrespective of any general incorporation language contained in such filing."

Exhibit 32.2

CERTIFICATION OF CHIEF FINANCIAL OFFICER
PURSUANT TO 18 U.S.C SECTION 1350,
AS ADOPTED PURSUANT TO
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

Pursuant to the requirement set forth in Rule 13a-14(b) of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), and Section 1350 of Chapter 63 of Title 18 of the United States Code (18 U.S.C. §1350), Bronson Crouch, Chief Executive Officer of Instil Bio, Inc. (the "Company"), hereby certifies that, to the best of his knowledge:

1. The Company's Annual Report on Form 10-K for the period ended December 31, 2021, to which this Certification is attached as Exhibit 32.1 (the "Annual Report") fully complies with the requirements of Section 13(a) or Section 15(d) of the Exchange Act, and

2. The information contained in the Annual Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

In Witness Whereof, the undersigned has set their hand hereto as of the March 7, 2022.

/s/ Sandeep Laumas

Sandeep Laumas

Chief Financial Officer

"This certification accompanies the Form 10-K to which it relates, is not deemed filed with the Securities and Exchange Commission and is not to be incorporated by reference into any filing of Instil Bio, Inc. under the Securities Act of 1933, as amended, or the Securities Exchange Act of 1934, as amended (whether made before or after the date of the Form 10-K), irrespective of any general incorporation language contained in such filing."