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The information in this preliminary prospectus supplement is not complete and may be changed. A registration statement has been filed with the Securities and Exchange Commission and is effective. This prospectus supplement is not an offer to sell these securities and it is not soliciting an offer to buy these securities in any jurisdiction where the offer or sale is not permitted.

Subject to Completion, dated February 28, 2023

PRELIMINARY PROSPECTUS SUPPLEMENT
(To Prospectus dated November 18, 2022)

$100,000,000

Common Stock

We are offering $100 million of shares of our common stock.

Our common stock is listed on The Nasdaq Global Select Market under the symbol "TSVT." The last reported sale price of our common stock on The Nasdaq Global Select Market on February 27, 2023 was $13.74 per share.

Investing in our common stock involves significant risks. See "Risk Factors" beginning on page S-15 of this prospectus supplement, page 2 of the accompanying base prospectus and in the documents incorporated by reference in this prospectus supplement for a discussion of the factors you should carefully consider before deciding to purchase our common stock.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or passed upon the adequacy or accuracy of this prospectus supplement or the accompanying base prospectus. Any representation to the contrary is a criminal offense.

	Per Share	Total
Public offering price	$	$
Underwriting discounts and commissions [(1)]	$	$
Proceeds to 2seventy bio, Inc. before expenses	$	$

(1) We have agreed to reimburse the underwriters for certain FINRA-related expenses. See "Underwriting" for additional information regarding the compensation payable to the underwriters.

We have granted the underwriters an option for a period of 30 days to purchase up to an additional shares of our common stock at the public offering price less the underwriting discount.

The underwriters expect to deliver the shares of common stock on or about , 2023.

Joint Book-Running Managers

Goldman Sachs & Co. LLC **Cowen** **SVB Securities**

Prospectus supplement dated , 2023

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PROSPECTUS SUPPLEMENT

PROSPECTUS

ABOUT THIS PROSPECTUS SUPPLEMENT

This document is part of a registration statement that we filed with the Securities and Exchange Commission, or the SEC, utilizing a "shelf" registration process and consists of two parts. The first part is this prospectus supplement, which describes the specific terms of this common stock offering and also adds to and updates information contained in the accompanying prospectus and the documents incorporated by reference herein. The second part, the accompanying prospectus, provides more general information. Generally, when we refer to this prospectus, we are referring to both parts of this document combined. To the extent there is a conflict between the information contained in this prospectus supplement and the information contained in the accompanying prospectus or any document incorporated by reference therein filed prior to the date of this prospectus supplement, you should rely on the information in this prospectus supplement; provided that if any statement in one of these documents is inconsistent with a statement in another document having a later date—for example, a document incorporated by reference in the accompanying prospectus—the statement in the document having the later date modifies or supersedes the earlier statement.

We further note that the representations, warranties and covenants made by us in any agreement that is filed as an exhibit to any document that is incorporated by reference herein were made solely for the benefit of the parties to such agreement, including, in some cases, for the purpose of allocating risk among the parties to such agreements, and should not be deemed to be a representation, warranty or covenant to you. Moreover, such representations, warranties or covenants were accurate only as of the date when made. Accordingly, such representations, warranties and covenants should not be relied on as accurately representing the current state of our affairs.

Neither we nor the underwriters have authorized anyone to provide any information other than that contained or incorporated by reference into this prospectus supplement, the accompanying prospectus or in any free writing prospectus prepared by or on behalf of us or to which we have referred you. We and the underwriters take no responsibility for, and can provide no assurance as to the reliability of, any other information that others may give you. This prospectus supplement and the accompanying prospectus do not constitute an offer to sell, or a solicitation of an offer to purchase, the securities offered by this prospectus supplement and the accompanying prospectus in any jurisdiction to or from any person to whom or from whom it is unlawful to make such offer or solicitation of an offer in such jurisdiction. The information contained in this prospectus supplement or the accompanying prospectus, or incorporated by reference herein or therein is accurate only as of the respective dates thereof, regardless of the time of delivery of this prospectus supplement and the accompanying prospectus or of any sale of our common stock. It is important for you to read and consider all information contained in this prospectus supplement and the accompanying prospectus, including the documents incorporated by reference herein and therein, in making your investment decision. You should also read and consider the information in the documents to which we have referred you in the sections entitled "Where You Can Find More Information" and "Incorporation of Certain Information By Reference" in this prospectus supplement and in the accompanying prospectus.

We are offering to sell, and seeking offers to buy, shares of our common stock only in jurisdictions where offers and sales are permitted. The distribution of this prospectus supplement and the accompanying prospectus and the offering of the common stock in certain jurisdictions may be restricted by law. Persons outside the United States who come into possession of this prospectus supplement and the accompanying prospectus must inform themselves about, and observe any restrictions relating to, the offering of the common stock and the distribution of this prospectus supplement and the accompanying prospectus outside the United States. This prospectus supplement and the accompanying prospectus do not constitute, and may not be used in connection with, an offer to sell, or a solicitation of an offer to buy, any securities offered by this prospectus supplement and the accompanying prospectus by any person in any jurisdiction in which it is unlawful for such person to make such an offer or solicitation.

For purposes of this prospectus supplement, references to the terms "TSVT," "the Company," "we," "us" and "our" refer to 2seventy bio, Inc., together with its subsidiaries, unless the context otherwise requires.

PROSPECTUS SUPPLEMENT SUMMARY

This summary highlights certain information about us, this offering and selected information contained elsewhere in this prospectus supplement, the accompanying base prospectus and in the documents we incorporate by reference. This summary is not complete and does not contain all of the information that you should consider before making an investment decision. You should read this entire prospectus carefully, especially the risks of investing in our common stock discussed under "Risk Factors" beginning on page S-15 of this prospectus supplement and page 2 of the accompanying base prospectus, along with our consolidated and combined financial statements and notes to those consolidated and combined financial statements and the other documents incorporated by reference in this prospectus supplement, along with any free writing prospectus that we have authorized for use in connection with this offering.

Company Overview

We are a cell and gene therapy company focused on the research, development, and commercialization of transformative treatments for cancer. We are led by an accomplished team with significant expertise and experience in this field, from discovery through clinical development to regulatory approval of *Abecma* (idecabtagene vicleucel, or ide-cel), the first chimeric antigen receptor ("CAR T") cell therapy approved by the U.S. Food and Drug Administration ("FDA") for multiple myeloma. Our approach combines our expertise in T cell engineering technology and lentiviral vector gene delivery approaches, experience in research, development, and manufacturing of cell therapies and a suite of technologies that can be selectively deployed to develop highly innovative, targeted cellular therapies for patients with cancer. We are advancing multiple clinical programs, including DARIC33, for the treatment of pediatric patients with relapsed and refractory acute myeloid leukemia and bbT369, for the treatment of patients with B-cell non-Hodgkins lymphoma as well as multiple preclinical programs, including bbT4015, an engineered CAR T cell therapy targeting MUC16. Additionally, together with our partner Bristol-Myers Squibb ("BMS") we are delivering *Abecma* to multiple myeloma patients in the United States following approval by the FDA of *Abecma* in March 2021 for the treatment of adults with multiple myeloma who have received at least four prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 (cyclic ADP ribose hydrolase) monoclonal antibody.

Our Approach

Our approach is to create product candidates that are multiplex engineered cell therapies by combining: (1) CAR and T cell receptor technology, which programs T cells to recognize and kill cancer cells based on the cell surface expression or presentation of intracellular protein targets, respectively; (2) dual-targeting CAR architecture for multi-target tumor cell recognition; (3) our core lentiviral gene transfer technology which delivers these genetic cargos (and more) to program a patient's own T cells to the kill the cancer cells; (4) our megaTAL-based gene-editing technology which allows us to perform site specific gene addition or deletion from the genome to improve the properties of the T cell; and (5) genetically encoded technologies for engineering T cells to enhance the cytotoxic activity and reprogram the tumor microenvironment for more effective anti-tumor responses. This approach is differentiated by: (1) careful analysis of clinical and correlative data with the goal of precisely defining the key attributes of a cellular therapy necessary for anti-tumor effect; (2) the ability to design and then engineer a cell with these key attributes; combined with (3) a technology suite capable of delivering multiple innovations within a single drug product.

We believe this approach will allow us to address the challenges of achieving deep and durable clinical benefit to patients with cancers. We believe the ability of tumors to evade the immune system and to escape the action of a single drug intervention can be addressed by cellular therapies pre-armed with multi-layered strategies for tumor eradication and control. These multiplex cell therapies may have the potential to achieve a depth and durability of response, independent of the tumor type, that is not measured in weeks, but in months or years. We believe that our approach will allow us to improve how cell and gene therapies are discovered, developed, and manufactured, with the potential to transform the care of patients with cancer. For example, bbT369, our product candidate for B-NHL, uses multiple technologies in order to address the two main modes of failure observed with CD19-targeted T cell approaches: loss or diminution of antigen expression and reduction in T cell activation through loss or diminution of co-receptor signaling.

We believe that our past experience in the clinical setting also provides us with a unique advantage, given the relative nascency of the CAR T cell field and the consequent paucity of large data sets of autologous cellular therapies in cancer. We, including through our collaborators at BMS, have treated hundreds of patients with multiple myeloma in the clinical setting, and the clinical and correlative data sets from our collaboration with BMS provide us with a deep understanding of the biology of the tumor itself, its interplay with immune cells, and which cell therapy attributes may be key to patient response. We believe that understanding is critical to identifying the key barriers in the treatment of the cancer. Specifically, we believe that understanding the heterogeneity of target expression combined with any tumor-specific mechanisms of immune evasion at play can help define the components of a cellular therapy with the potential for maximal anti-tumor activity. This understanding will be key to our product candidate design and selection, manufacturing process design and execution, and clinical trial design and development strategy.

In designing our next-generation product candidates, we start with the concept of a tumor-redirected T cell (via CAR or engineered T cell receptor, or TCR, technology) and then add one or more additional features or components from the suite of proprietary technologies we have developed with the purpose of overcoming specific limitations of first-generation T cell therapies. For example, these additional technologies may address:

- Tumor targets with off-tumor expression, through the application of our regulatable CAR T technology, dimerizing agent–regulated immunoreceptor complex, or DARIC;
- Immunosuppressive molecules in the tumor microenvironment, through the application of our chimeric TGFβ flip receptor, or CTBR, technology which turns a suppressive signal into a T cell supportive interleukin receptor signal;
- Antigen loss or down-regulation resulting in escape, through application of our dual-targeting CAR T cell technology; or
- Incomplete T cell activation or proliferation resulting in a loss of T cell potency, through the implementation of synergistic co-stimulatory pathways and the application of our gene-editing technology to knock-out intracellular checkpoints.

Our clinical programs in B-NHL and AML are illustrations of our multiplex approach, applied to address the specific challenges of treating those cancers:

We are developing our bbT369 product candidate as a potential treatment for patients with B-NHL. The advent of the first generation of anti-CD19 CAR T products represents a significant advancement in the field of B-NHL and has established a new standard for the treatment of patients with relapsed and refractory B-NHL. However, more than half of patients treated with an anti-CD19 CAR T do not achieve durable remission. Prognosis remains poor for these patients, with median overall survival after axicabtagene ciloleucel, or axi-cel, of approximately six months for patients initially responding and less than two months for patients without initial response. The main limitations of the first-generation CAR T therapies are the lack of complete response in some patients and the potential for late relapse, indicating a need for deeper and more durable treatment responses. We take a differentiated approach from the approved anti-CD19 CAR T therapies: we have designed a dual-targeting CAR to target CD20 and CD79a to limit antigen escape (as has been seen with CD19-targeted therapies). We provide split co-stimulation to drive maximal activation of the T cell in response to antigens. We include a gene edit designed to drive increased expansion, resist anergy, and maintain potency in sub-optimal conditions for T cell activation. Clinical study CRC-403, an open-label, multi-site Phase 1/2 dose-escalation study of bbT369, will serve as a potential proof-of-concept assessment of our proprietary gene editing platform, dual-targeting strategies and split co-stimulation signaling technology. Dosing in the first cohort of CRC-403 was completed in 2022, and the trial is currently enrolling patients at the second dose level.

We are developing our SC-DARIC33 product candidate as a potential treatment for pediatric and young adult patients with relapsed or refractory AML. Although CAR T therapy has shown transformative potential and durable efficacy in other hematologic tumors, the use of CAR T therapy in the treatment of AML has been complicated by the expression of key targets such as CD33 across healthy myeloid cells in addition to leukemic blasts and stem cells. In other words, a highly potent CAR T cell directed towards one of these targets carries the significant risk of

"on-target, off-tumor" toxicity because of broad myeloid aplasia. In developing SC-DARIC33 as a potential treatment for patients with AML, we seek to address the challenge of balancing potency and safety risk by combining advanced CAR T receptor technology with our DARIC technology, a pharmacologically controlled "on-off" switch to reversibly regulate the activity of the CAR T cell. We have designed the CAR to target both full-length and alternatively spliced CD33 variants to address heterogeneity in the disease, and to reduce the risk of antigen escape and disease relapse. We believe that the DARIC switch will give treating physicians the ability to turn off highly potent CAR T cell activity to allow for myeloid recovery, while being able to re-activate CAR T cell activity on demand. PLAT-08, the investigator-initiated proof-of-concept Phase 1 clinical trial of our SC-DARIC33 product candidate in pediatric and young adult relapsed or refractory AML patients, is led by our partner Seattle Children's Therapeutics, a non-profit enterprise associated with Seattle Children's Research Institute, or SCRI. The PLAT-08 trial is nearing completion of the mandatory adult dosing phase, and the totality of initial data to-date suggests SC-DARIC33 activation by rapamycin. The PLAT-08 trial will allow us to further assess our DARIC platform in light of the rapamycin-induced activation of SC-DARIC33 and potential for marrow recovery following rapamycin withdrawal.

Our Strengths

We believe that the capabilities and experience that our team has accrued provide us with an opportunity to capitalize on recent progress in the understanding of genetics, gene-editing, gene expression, tumor biology, immunology, process analytics, computational biology and data analytics to discover, develop and bring to the market next-generation cell and gene therapies for cancer:

- Extensive suite of gene modification technologies allows us to create multiplex product concepts: We have access to a broad range of technologies that we can leverage to design product candidates that aim to address the challenges of specific cancers. With internal capabilities to knock-in, knock-out, modify, and control expression of genes across multiple modalities with gene addition, gene-editing, cell engineering, and synthetic biology approaches, we have the ability to apply a combination of technologies to design potential multiplex next-generation cell and gene therapies for cancer.

- Deep clinical experience and expertise with data science-driven iteration: From having treated hundreds of patients with multiple myeloma in CAR T programs through our collaboration with BMS, we have gained a deep understanding of cell therapy itself as well as an appreciation for the value of iterating on clinical data to inform our product candidate design, selection, manufacturing, clinical trial design and development strategy. Additionally, we employ data analytics in manufacturing to understand the critical product attributes of successful cellular products.

- Manufacturing experience and capability: Our team has accumulated significant experience in the manufacturing, analytical testing, and quality aspects from both lentiviral vectors and autologous lentiviral vector-transduced cellular drug products, from shepherding *Abecma* through clinical development, regulatory approval, and to commercialization in the United States, as well as from bluebird bio's betibeglogene autotemcel in Europe. Moreover, we, in partnership with Resilience, have successfully scaled-up our suspension-based manufacturing process for lentiviral vector, or sLVV, which is being utilized in ongoing clinical trials for ide-cel. We recently added a Phase 1 cell therapy manufacturing facility in our Cambridge headquarters which we believe will enable us to improve the profile and accelerate timelines for the delivery of product candidates to patients. We anticipate the facility will be operational in 2023. We believe our experience spanning first-in-human to commercial manufacturing, quality control and quality assurance represents know-how critical to the efficient translation and development of our multiplex product candidates.

- Collaboration and connectivity: We have a strategic network of collaborations across industry, academic scientists, and medical experts to access technologies and expertise that supplement our proprietary technologies. We believe these collaborations and partnerships provide us with a rich suite of technologies permitting the design of impactful multiplex product candidates.

Our Strategy

Our strategy is to apply our broad range of technologies to design multiplex product candidates that address the key treatment challenges in cancer. Unlike other oncology-focused companies in our space, we believe our breadth of technology enables us to develop tailored products focused on the specific areas of cancer biology we have identified. We selectively combine the relevant features and components from our range of tools and technologies to address the defined attributes of a cellular therapy that we believe are necessary for anti-tumor effect.

To execute on our strategy, we plan to:

- Co-commercialize *Abecma*, including clinical expansion to earlier lines of therapy, through our collaboration with BMS, and leverage our clinical and operational experience under this collaboration and this product revenue stream to further invest in our next-generation proprietary programs.
- Leverage our leadership position in autologous CAR T therapies to advance through the clinic our next-generation programs in B-NHL, AML, and multiple myeloma.
- Apply our multiplex approach to the discovery and design of transformative cell and gene therapy products for the treatment of solid tumors.
- Seek to extend our approach to other cell types beyond T cells and to include off-the-shelf approaches, as we gain additional experience in our autologous T cell programs.
- Build upon our existing internal lentiviral vector manufacturing know-how and experience through both selective investments in manufacturing collaborations and through our internal capabilities, including the build-out of our drug product manufacturing capabilities at our Cambridge, Massachusetts headquarters. The facility, which we anticipate will be operational in 2023, is designed to enable rapid translational research in our clinical trials, as well as allow us to manufacture drug product for preclinical and Phase 1 clinical development activities, over time, with the objectives of enabling rapid iteration on clinical learnings into research and development, increasing the efficiency of manufacturing processes, and improving the overall patient and healthcare professional experience.

Our Technologies

Our oncology programs use a lentiviral vector to deliver the genetic cargo with the potential to program a patient's own T cells to recognize specific proteins or protein fragments on the surface of cancer cells to kill the cancer cells. Our current programs are based on CAR technology designed to program T cells to recognize cancer cells based on expression of specific cell surface antigens, and T cell receptor technology designed to program T cells to recognize cancer cells based on protein fragments derived from either intracellular or extracellular proteins displayed on the tumor cell surface. The genetically engineered T cells are designed to supplement a patient's immune system and we believe they have the potential to be further engineered to overcome immune evasion mechanisms employed by cancer cells. Our approach is to create multiplex engineered cell therapies by combining our foundational lentiviral vector and CAR/TCR technology with next-generation tools to address the challenges in existing cancer treatments.

- *Dual-Targeting.* Polyclonal responses are a hallmark of adaptive immunity, but most T cell therapies have been devised with antigen receptors specific to a single target antigen. There are many documented cases of cancer deploying its intrinsic genetic plasticity to escape mono-targeted T cell therapies (both with cellular and more classical modalities, such as small molecules and antibodies). In such cases, our solution is to utilize a dual-targeting antigen receptor, including a multi-chain, dual-targeting architecture, to respond when either target antigen is present on a cancer cell, as well as an architecture that leverages the unique properties of humanized single-domain camelid-derived antibodies.
- *DARIC*. We have developed a dimerizing agent–regulated immunoreceptor complex, which we refer to as DARIC, that comprises separate antigen targeting and signal transduction componentry. DARIC receptors become poised for anti-tumor function only when the two components are brought together as

heterodimers, a process that is strictly dependent on the bridging function of the drug rapamycin. This technology can enable pharmacological, "on-demand" control of engineered T cell responses. Controlling the "on" and "off" states of engineered T cells also creates opportunities to pursue cancers and cancer targets with disease characteristics and expression profiles that are incompatible with constitutively responsive antigen receptors.

- *Reversal of immunosuppression*. Patients who present in the clinic with advanced metastatic disease host tumors that have evolved to evade endogenous immunity via a variety of mechanisms. Tumor infiltrating T cells lose potency over time due to repetitive antigen stimulation and exhaustion in a tumor microenvironment that suppresses T cell function. Checkpoint engagement, hypoxia, poor nutrient conditions, and exposure to immunosuppressive cell types and cytokines all significantly blunt T cell potency and thwart attempts to regress tumors in clinically meaningful ways. We have developed a suite of synthetic biology innovations that antagonize and rewire immunosuppressive signaling and response pathways. We have focused significant attention on TGFβ, a profoundly immunosuppressive cytokine found at high levels in many solid tumors. Our chimeric TGFβ flip receptor, or CTBR, technology converts this suppressive signal into a supportive interleukin receptor signal that enhances T cell function. Suppressive to enhancing signal conversion operates in a localized, engineered T cell intrinsic manner, enhancing potency within the microenvironment of the tumor where the highest concentrations of activated TGFβ ligand are present. We have also developed several approaches to modulate T cell metabolism to allow for enhanced function and potency in the metabolically challenging tumor microenvironment.

- *Co-stimulation*. Parallel track costimulatory domains, also known as chimeric costimulatory receptors, offer a unique set of functional attributes that culminate in enhanced anti-tumor activity. This technology pairs enhanced targeting breadth with a qualitatively distinct and more potent functional response, simultaneously countering two potential mechanisms of resistance.

- *Gene-editing*. megaTALs are highly specific, compact nucleases that efficiently catalyze the formation and mutagenic resolution of double-stranded breaks at pre-specified genetic target sequences. Using our megaTAL gene-editing platform, we have demonstrated that disrupting genes that intersect with T cell signaling and response pathways can promote more potent immune responses. In addition, we have developed a full suite of on-target editing assays, functional bioassays, and off-target discovery and verification analytics to deeply characterize gene-editing events and their functional consequences in target cells, which may enable the potential application of this technology in the clinical setting.

- *mRNA capabilities*. We have also developed messenger RNA, or mRNA capabilities that enable transient gene expression, both in cells cultured ex vivo and for organ-specific in vivo delivery. We manufacture mRNA starting from a proprietary plasmid template outfitted with an encoded poly-A tract, an approach that results in highly homogenous mRNA species following in vitro transcription. Our purification process includes double-stranded RNA, or dsRNA depletion steps to minimize immunogenicity and optimize cell viability. A robust suite of analytical assays is in place to ensure that consistently pure and potent material is generated. We have developed clinical-scale electroporation processes for ex vivo mRNA delivery and are actively using these processes to improve T cell potency via our megaTAL gene-editing platform. This technology can potentially be further leveraged to transiently express other factors that may be advantageous to ex vivo manufactured T cells.

In addition, we continue to invest in our core foundational technologies and build upon our leadership position in autologous engineered cell therapy products based on CAR and TCR approaches.

- *Next-generation lentiviral vector design*. With a management team that collectively possesses decades of experience in this technology, we have extensively refined the componentry and methodology behind lentiviral vector design and manufacturing. Our transfer plasmid design elements include several innovations that have created advanced gene expression tuning capabilities and the delivery of large and complex genetic payloads via transgene stacking. We have developed proprietary codon optimization algorithms, promoter variants, and regulatory elements that we believe together enable constitutive and/or responsive expression profiles across a range of transgene expression levels. These mature capabilities

enable highly efficient transfer of sophisticated genetic modules, such as the multiplex product concepts represented by our next-generation programs.

- *Target selection and validation*. Cancer targets with profiles that make them appropriate for cell therapy development have diverse structural features, biochemical properties, and sub-cellular distribution characteristics. To support novel target identification, we have developed significant in-house expertise and external collaborations in the areas of data mining, functional genomics, and primary tissue analysis. We have also built a full suite of target validation assays to perform confirmatory studies assessing tumor and normal tissue expression properties. In addition, we have developed significant internal expertise specifically aimed at de-risking potential off-target liabilities of TCR engineered T cells. We have focused the bulk of our efforts on select hematological and solid tumor indications. We believe this approach allows us to deeply interrogate the target landscape in cancers where T cell therapies may have the highest potential for technical success.

- *Receptor engineering*. We have access to state-of-the-art binder capabilities through our collaboration arrangements that cover the full range of potential cancer targets. For intracellular targets of interest, our partners develop TCRs and fully humanized "peptide-in-groove", or PiG, single-chain variable fragment, or scFv, reagents. For surface proteins, we have multiple providers of immunization-sourced, fully humanized scFv and single-domain reagents.

- *Manufacturing process innovations*. Our analytical development, clinical bioassays, correlative research, and data sciences teams have exceptional access to clinical trial data using CAR T therapies. We are regularly interrogating these data sets to isolate key manufacturing variables and correlates of clinical signals that enable hypothesis testing. These activities derive insights that inform process research directions for optimizing T cell manufacturing through reagents, processes, and culture timing, and for the discovery of underlying biological relationships between clinical and correlative data.

Our Programs

B-Cell Non-Hodgkin's Lymphoma

We are developing our bbT369 product candidate as a treatment for patients with B-NHL, a heterogeneous group of neoplasms that can result in enlarged nodes across the body, neck, and abdomen, often coinciding with "B-symptoms" that are significant to the prognosis and staging of the disease, such as fever, drenching night sweats, and rapid and extreme weight loss. B-cell NHLs represent more than 85% of all NHL cases worldwide, and we plan to develop bbT369 to treat several subtypes of B-cell NHLs, specifically diffuse large B-cell lymphoma, or DLBCL, high-grade B-cell lymphoma, or HGBCL, primary mediastinal large B-cell lymphoma, or PMBCL, follicular lymphoma, or FL, or transformed follicular lymphoma, or TFL. DLBCL is the most common form of NHL, accounting for a third of all NHL cases, with annual incidence in the United States estimated at approximately 25,000. DLBCL is a particularly aggressive form of NHL that requires immediate therapy upon diagnosis (with a median overall survival of less than one year in untreated patients).

Our multiplex approach is intended to enhance the depth and duration of response in patients currently underserved by existing options. bbT369 is a non-CD19-containing CAR T that addresses the limitations of the currently available therapies by using unique layered technologies, designed with the following key features:

- A novel combination of CD20 and CD79a targets that are co-expressed in many B-NHL tumors to both allow treatment of CD19 negative / CD19 low tumors and to limit the potential for antigen escape;

- Split co-stimulation to drive optimal and complete immune signaling; and

- A gene edit to drive increased expansion, resist anergy, and maintain potency in sub-optimal tumor conditions.

In preclinical models, bbT369 clears a variety of B-NHL tumors, including both dual and single target positive tumors, and outperforms CD19 in cells with varying levels of antigen expression. Additionally, the gene edit

demonstrates increased cytokine production and expansion in vitro, and when compared to the same dual-targeted, but unedited, construct, bbT369 results in a lower rate of late tumor relapses.

Dosing in the first cohort of clinical study CRC-403, an open-label, multi-site Phase 1/2 dose-escalation study of bbT369 in relapsed and/or refractory B-NHL after autologous SCT or two or more prior lines of therapy, was completed in 2022. There have been no dose-limiting toxicities observed to-date. The manufacturing success rate was high and turnaround time was in line with other autologous CAR Ts despite the additional complexity of the product candidate. CRC-403 will serve as a potential proof-of-concept assessment of our proprietary gene editing platform, dual-targeting strategies and split co-stimulation signaling technology. Multiple clinical trial sites are currently recruiting patients who are either naïve to CD19 CAR T or who have relapsed after CD19 CAR T in the second dose level of the trial. The Phase 1 portion will be a dose-escalation study, with the phase 2 stage allowing continued investigation of these two different patient populations at the recommended dose. The trial will be conducted at four study sites.

Acute Myeloid Leukemia

We are developing our SC-DARIC33 product candidate for the treatment of patients with acute myeloid leukemia (AML). Systemic therapy (including chemotherapy, hypomethylating agents, and targeted biologics) alongside hematopoietic stem cell transplant (HSCT) are the mainstays of AML treatment today. Of note, many adult patients are unfit for such intensive therapy, which in turn leads to less favorable clinical outcomes. Though HSCT provides meaningful clinical benefit to those who are eligible, the unmet need in this heterogenous and aggressive disease remains high. Prognosis is typically poor for adult patients, with a 5-year survival rate of 10-35% depending on disease subtype. In children and adolescents, the 5-year survival rate is 50 to 70%, with variation by subtype and other risk factors as seen in adults. Of note, median overall survival in adults with relapsed and refractory AML is less than 12 months, indicating a particularly high unmet need for these patients.

Although CAR T therapy has shown transformative potential and durable efficacy in other hematologic tumors, their use in the treatment of AML is complicated by the expression of key AML targets, such as CD33, across healthy myeloid cells in addition to leukemic blasts and stem cells. Thus, a highly potent CAR T cell directed towards one of these targets carries the potential risk of significant “on-target, off-tumor” toxicity because of broad myeloid aplasia. Achieving durable remission with a CAR T while balancing the safety risks is a critical challenge for the treatment of AML with CAR T therapy.

We seek to address this challenge with our SC-DARIC33 product candidate, which combines CAR T technology with DARIC, our dimerizing agent-regulated immunoreceptor complex technology. In our SC-DARIC33 product candidate, the traditional components of an anti-CD33 CAR are separated into two subunits which only enable T cell activation in the presence of sub-immunosuppressive doses of rapamycin, an orally-administered small molecule, which functions as an “on-off” toggle switch. In vitro and in vivo studies have shown that this regulated activation is reversible upon withdrawal of rapamycin and can be subsequently re-activated upon re-administration of rapamycin. Our SC-DARIC33 product candidate is designed to utilize this on-off toggle switch in the context of an autologous CD33-directed DARIC-T cell to drive deep responses in AML while “on” and allow myeloid compartment recovery while “off”.

In collaboration with Seattle Children’s Therapeutics, we are enrolling patients in PLAT-08, an investigator-initiated single-center proof-of-concept Phase 1 clinical trial of SC-DARIC33 in pediatric and young adult relapsed or refractory AML patients. This dose-finding trial is aimed at establishing safety, manufacturability, and early efficacy signals for SC-DARIC33 and we expect to conduct correlative analyses to confirm rapamycin-driven regulation in humans. We are nearing completion of the mandatory adult dosing phase, and the totality of the initial data suggests SC-DARIC33 activation by rapamycin. In parallel, we are also advancing next-generation, preclinical product concepts for pediatric and adult AML in partnership with SCRI. These concepts include multiplex targeting and additional enhancement technologies to address the heterogeneity of disease and prevent relapse. Specifically, a next-generation AML product concept has been selected and will enter non-clinical development in 2023. This new candidate is built off of our new RESET receptor architecture and incorporates dual targeting along with a potency enhancement while retaining the DARIC-like drug regulation. The terms of our arrangements with Seattle

Children's Therapeutics and SCRI are described more fully below under "Strategic Collaborations—Seattle Children's."

Multiple Myeloma

Through our collaboration with BMS, *Abecma* (ide-cel) is our lead program in multiple myeloma. The terms of our arrangements with BMS are described more fully below under "Strategic Collaborations—BMS." We are also conducting next-generation discovery programs in multiple myeloma on our own.

Abecma and our collaboration with BMS. In March 2021, *Abecma* (idecabtagene vicleucel; ide-cel) was approved by the FDA in the United States for the treatment of adults with multiple myeloma who have received at least four prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor, and an anti-CD38 monoclonal antibody. *Abecma* is a first-in-class B cell maturation antigen, or BCMA, CAR T therapy for the treatment of multiple myeloma, and represents our first oncology product candidate that has progressed from bluebird bio's internal research programs, through clinical development to approval and commercialization, together with our collaboration partner, BMS. Gross revenue from sales of *Abecma* in the United States in 2022 equaled $297 million, which is shared equally between us and BMS along with the related cost of sales and other commercialization costs. Together with BMS, we are in the process of increasing U.S. testing and manufacturing capacity, and therefore overall U.S. supply chain capacity, for *Abecma*.

BCMA is a cell surface protein that is nearly universally expressed on cancer cells in multiple myeloma, and on normal plasma cells and mature B cells, but not other cells. As the first CAR T cell therapy approved for multiple myeloma, *Abecma* is a potentially transformative, single-infusion, individualized treatment that offers patients who have limited effective treatment options the potential for long-term disease control. The approval of *Abecma* in the United States was based on positive results from the pivotal KarMMa study. In the KarMMa study, the overall response rate was 73%, and 33% of patients achieved a complete response. Onset of response was rapid with a median time to first response of one month. Median duration of response was 10.7 months and 19 months for those who achieved a complete response. *Abecma* has a well-established safety profile with mostly low-grade cytokine release syndrome (Grade ≥3: 5%; grade ≤2 events: 84%) and neurologic toxicities (Grade ≥3: 3%; grade ≤2 events: 18%) with early onset and resolution. Results from the KarMMa study were published in the February 24, 2021 issue of the New England Journal of Medicine. The FDA and EMA have granted Orphan Drug status to ide-cel for the treatment of patients with relapsed and refractory multiple myeloma. The EMA has granted PRIME eligibility to ide-cel for relapsed and refractory multiple myeloma. BMS is conducting studies to support the use of *Abecma* in earlier lines of therapy. Our and BMS' broad clinical development program for *Abecma* includes ongoing clinical trials in earlier lines of treatment for patients with multiple myeloma, including newly diagnosed multiple myeloma.

Additionally, under the collaboration arrangement with BMS, we have an option to co-develop and co-promote bb21217, an investigational BCMA-targeted CAR T cell therapy, within the United States. However, following our review of data from the CRB-402 clinical trial, and based in part on the strength of *Abecma* clinical data and commercial sales to date, we, together with BMS, do not intend to pursue further development of bb21217.

Next-generation approaches. Our next-generation multiple myeloma program strategy is focused on leveraging our clinical experience from *Abecma* and bb21217, translational and correlative data, and technology platforms to solve definable and meaningful problems in the field. Leveraging our leadership in autologous CAR T therapy, our next-generation autologous multiple myeloma program utilizes multiple technologies including process improvements and dual targeting, with the goal of achieving best-in-class efficacy through deeper and more durable responses than the current generation of autologous CAR T products.

Solid Tumors

Our research-stage programs in solid tumors include tumors expressing the MUC16 antigen and tumors expressing the MAGE-A4 antigen, among others.

MUC16. Together with our partner Regeneron Pharmaceuticals, Inc., or Regeneron, we are advancing our bbT4015 product candidate, an engineered T cell therapy targeting MUC16, through preclinical studies. We anticipate submitting an Investigational New Drug Application, or IND, for a clinical trial bbT4015 in patients with

ovarian cancer in 2023. This first in-human study will prospectively include combination agents, including those in Regeneron's pipeline, and will be the first program to utilize our new in-house drug product manufacturing facility.

MUC16 is a large extracellular protein expressed on over 80% of ovarian tumors, including all ovarian subtypes. Its overexpression in tumors and relatively lower expression on normal tissues makes MUC16 an attractive ovarian cancer target for cellular therapies and a logical fit for the deployment of orthogonal enhancement strategies. Our MUC16 program incorporates a highly potent CAR T that targets a region close to the transmembrane ("nub" region) of MUC16 and is not inhibited by the presence of high concentrations of CA-125. Encouraging preclinical data suggests that T cells expressing the "nub"-directed MUC16 CAR T are able to clear tumors in a highly stringent ovarian cancer tumor rechallenge xenograft mouse model. We intend to combine this potent CAR T with a titratable pharmacologic agent with the goal of enhancing tumor control.

MAGE-A4. Over ten types of solid tumors express the MAGE-A4 antigen, making it a promising target for cell therapy, including lung, head and neck, gynecologic and gastric cancers. Together with our partner Regeneron we are advancing an engineered TCR therapy targeting MAGE-A4 through preclinical studies. We believe our MAGE-A4 program has the potential to address the challenges of solid tumors in a three-pronged way: (1) we have identified a potent T cell receptor targeting a prevalent intracellular peptide antigen from MAGE-A4, (2) engineered this receptor for a strong anti-tumor response, and (3) incorporated an innovative switch receptor (CTBR12) that converts the highly suppressive TGFβ signal in the hostile tumor microenvironment into a potent T cell intrinsic activation signal. The TGFβ signaling pathway has been broadly implicated as a key suppressive factor in the TME of multiple MAGEA4+ indications, including non-small cell lung, bladder, ovarian, and head and neck carcinomas. In 2022, we entered into an agreement with JW (Cayman) Therapeutics Co. Ltd., or JW Therapeutics, to clinically evaluate this potency enhanced MAGE-A4 TCR program. JW Therapeutics plans an investigator-initiated trial in China in 2023, initially focused on esophageal carcinoma.

Hemophilia A

Together with our partners Novo Nordisk A/S ("Novo Nordisk") and Genevant Sciences Corporation ("Genevant"), we are also conducting preclinical studies of our product candidate in hemophilia A. Hemophilia A is a serious and rare inherited disease characterized by insufficient blood clotting that results from the lack of functional factor VIII, or FVIII. Hemophilia A is caused by mutations in the gene that encodes the coagulation FVIII protein. Our approach employs our gene editing technology (megaTALs) to insert a corrective copy of the FVIII gene directly into the genome of liver cells. We believe that this targeted integration approach may result in permanently corrected cells that have the potential to provide durable expression of therapeutic levels of FVIII protein.

Corporate Information

2seventy bio, Inc. was incorporated in the State of Delaware on April 26, 2021 for the purpose of holding bluebird bio, Inc.'s oncology portfolio and programs in connection with the separation of bluebird bio's oncology portfolio and programs from its severe genetic disease portfolio and programs. The contribution of this business to us occurred over a period of time prior to the completion of the separation, and we had no operations prior to such contribution. In that regard, on November 3, 2021, we entered into a separation agreement with bluebird bio, and on November 4, 2021, each bluebird bio stockholder received a pro rata share of 2seventy bio's common stock for every share of bluebird bio common stock held of record at the close of business on the record date for such distribution. As a result of such distribution, 2seventy bio became an independent, publicly traded company.

The address of our principal executive offices is 60 Binney Street, Cambridge, Massachusetts 02142 and our telephone number is (339) 499-9300. We also maintain a website at www.2seventybio.com. The information contained in or accessible from our website is not incorporated into this prospectus supplement, and you should not consider it part of this prospectus supplement. We have included our website address in this prospectus supplement solely as an inactive textual reference. Our common stock is listed on the Nasdaq Global Select Market under the symbol "TSVT."

We own various U.S. federal trademark applications and unregistered trademarks, including our company name. All other trademarks or trade names referred to in this prospectus supplement are the property of their respective

owners. Solely for convenience, the trademarks and trade names in this prospectus supplement are referred to without the symbols ® and ™, but such references should not be construed as any indicator that their respective owners will not assert, to the fullest extent under applicable law, their rights thereto.

Risks Associated with Our Business

- We are a cell and gene therapy company with a limited operating history as an independent company. To date, we have not recognized any revenues from the sale of products by us. Our revenues have been derived from out-licensing arrangements and collaboration arrangements, including the collaboration revenue derived from sales of *Abecma* by BMS. We may never become profitable.
- We have incurred significant operating losses in recent periods and anticipate that we will incur continued losses for the foreseeable future.
- We will require additional capital to finance our operations, which may not be available to us on acceptable terms, or at all. If we are unable to raise capital when needed or on attractive terms, we would be forced to delay, scale back or discontinue some of our product candidate development programs or pre-commercialization efforts.
- We depend heavily on the success of our lead product candidates, SC-DARIC33 and bbT369. We cannot be certain that we will be able to obtain regulatory approval for, or successfully commercialize, any of our current or future product candidates.
- If we experience delays or difficulties in the enrollment of patients in clinical trials, our receipt of necessary regulatory approvals could be delayed or prevented.
- Our current or future product candidates may cause adverse or other undesirable side effects that could delay or prevent their regulatory approval, limit the commercial profile of an approved label, or result in significant negative consequences following marketing approval, if any.
- If we are not able to obtain, or if there are delays in obtaining, required regulatory approvals both for our current or future product candidates, we will not be able to commercialize, or will be delayed in commercializing, our current or future product candidates, and our ability to generate revenue will be materially impaired.
- Even if we receive regulatory approval for any of our current or future product candidates, we will be subject to ongoing obligations and continued regulatory review, which may result in significant additional expense. Additionally, our current or future product candidates, if approved, could be subject to labeling and other restrictions and market withdrawal and we may be subject to penalties if we fail to comply with regulatory requirements or experience unanticipated problems with our drugs.
- Manufacturing our current or future product candidates is complex and we may encounter difficulties in production. If we encounter such difficulties, our ability to provide supply of our current or future product candidates for preclinical studies and clinical trials or for commercial purposes could be delayed or stopped.
- We rely, and expect to continue to rely, on third parties to conduct our ongoing and planned clinical trials for our current and future product candidates. If these third parties do not successfully carry out their contractual duties, comply with regulatory requirements or meet expected deadlines, we may not be able to obtain marketing approval for or commercialize our current and potential future product candidates and our business could be substantially harmed.
- We may experience business interruptions or negative market conditions arising out of global crises, including international conflicts, the ongoing COVID-19 global pandemic, or similar public health crises. Such events could cause a disruption of the development of our product candidates and adversely impact our business. Such events may contribute to global market conditions that negatively impact our ability to raise needed capital on favorable terms and timelines.

- If we are unable to obtain and maintain patent and other intellectual property protection for our technology and product candidates or if the scope of the intellectual property protection obtained is not sufficiently broad, our competitors could develop and commercialize technology and drugs similar or identical to ours, and our ability to successfully commercialize our technology and drugs may be impaired.

Implications of Being an Emerging Growth Company

We qualify as an "emerging growth company" as defined in the Jumpstart Our Business Startups Act of 2012, as amended (the "JOBS Act"). As an emerging growth company, we may take advantage of specified reduced disclosure and other requirements that are otherwise applicable generally to public companies. These provisions include:

- being permitted to only disclose two years of audited financial statements in addition to any required unaudited interim financial statements with correspondingly reduced "Management's Discussion and Analysis of Financial Condition and Results of Operations" disclosure;
- reduced disclosure about our executive compensation arrangements;
- not being required to hold advisory votes on executive compensation or to obtain stockholder approval of any golden parachute arrangements not previously approved; and
- an exemption from the auditor attestation requirement in the assessment of our internal control over financial reporting.

We would cease to be an emerging growth company on the date that is the earliest of (i) the last day of the fiscal year in which we have total annual gross revenue of $1.235 billion or more; (ii) the last day of the fiscal year following the fifth anniversary of the date of the first sale of common equity securities pursuant to an effective registration statement; (iii) the date on which we have issued more than $1.0 billion in nonconvertible debt during the previous three years; or (iv) the last day of the fiscal year in which we are deemed to be a large accelerated filer under the rules of the SEC, which means the market value of our common stock that is held by non-affiliates exceeds $700 million as of the prior June 30th. We may choose to take advantage of some but not all of these accommodations. We have taken advantage of reduced reporting requirements in this prospectus supplement. Accordingly, the information contained herein may be different from the information provided by other public companies that cannot or do not take advantage of reduced disclosure provision.

THE OFFERING

Common stock offered by us	shares of our common stock.
Option to purchase additional shares	The underwriters have a 30-day option to purchase up to an additional shares of common stock.
Common stock to be outstanding immediately after this offering	shares (shares if the underwriters exercise their option to purchase additional shares in full).
Use of Proceeds	We estimate that the net proceeds to us from this offering will be approximately $ million, or approximately $ million if the underwriters exercise their option to exercise their option to purchase additional shares in full. We currently intend to use the net proceeds from this offering, together with our existing cash, cash equivalents and marketable securities for research and development and clinical development costs to support the advancement of our product candidates and the expansion of our research and development programs; advancement of the KarMMa trials to support the use of *Abecma* in earlier lines of therapy, pursuant to our cost sharing arrangements with BMS; commercial activities in support of *Abecma*; working capital; capital expenditures; corporate development; and other general corporate purposes. See "Use of Proceeds" in this prospectus supplement for more information.
Risk factors	You should read the "Risk Factors" in this prospectus supplement, the accompanying base prospectus, and the risks set forth under the caption "Item 1A. Risk Factors" included in our Annual Report on Form 10-K for the fiscal year ended December 31, 2021 and the other documents incorporated by reference into this prospectus supplement for a discussion of factors to consider carefully before deciding to purchase shares of our common stock.
Nasdaq Global Market Symbol	TSVT

The number of shares of our common stock shown above to be outstanding immediately after this offering is based on 37,912,215 shares of common stock outstanding as of September 30, 2022 and excludes the following:

- 2,606,833 shares of common stock issuable upon exercise of options outstanding under our 2021 Stock Option and Incentive Plan at a weighted-average exercise price of $69.72 per share as of September 30, 2022;
- 1,331,817 shares of common stock issuable upon vesting and settlement of restricted stock units under our 2021 Stock Option and Incentive Plan as of September 30, 2022;
- 757,575 shares of common stock issuable upon the exercise of pre-funded warrants to purchase shares of common stock at an exercise price of $0.0001 per share outstanding as of September 30, 2022;
- 1,575,806 shares of common stock reserved for future issuance under our 2021 Stock Option and Incentive Plan as of September 30, 2022; and
- 200,625 shares of common stock reserved for future issuance under our 2021 Employee Stock Purchase Plan as of September 30, 2022.

Unless otherwise indicated, all information in this prospectus supplement:

- assumes no exercise of the outstanding stock options, settlement of the RSUs or exercise of the pre-funded warrants described above;
- assumes no exercise by the underwriters of their option to purchase additional shares of our common stock in this offering, and does not reflect the potential issuance of shares of our common stock that remain available for sale as of the date of this prospectus supplement under our "at-the-market" offering program, pursuant to which we may sell common stock for remaining gross proceeds of up to $150 million from time to time under our sales agreement with Cowen and Company, LLC.

RISK FACTORS

Investing in our common stock involves a high degree of risk. You should carefully consider the risks and uncertainties described below together with all of the other information contained in this prospectus supplement and the accompanying base prospectus and the risk factors in our most recent Annual Report on Form 10-K, our most recent Quarterly Report on Form 10-Q, together with other information in this prospectus supplement, the accompanying base prospectus and the information and documents incorporated by reference in this prospectus supplement and the accompanying base prospectus, and in any prospectus supplement or free writing prospectus that we authorize for use in connection with this offering. If any of the following risks actually occur, our business, prospects, operating results and financial condition could suffer materially. In such event, the trading price of our common stock could decline and you might lose all or part of your investment.

Risks Related to This Offering

The sale of a substantial number of shares of our common stock, including by us, could cause the market price of our common stock to drop significantly, even if our business is doing well.

Sales of a substantial number of shares of our common stock in the public market, or the perception in the market that the holders of a large number of shares intend to sell shares, could reduce the market price of our common stock. Persons who were our stockholders prior to our initial public offering continue to hold a substantial number of shares of our common stock. If such persons sell, or indicate an intention to sell, substantial amounts of our common stock in the public market, the trading price of our common stock could decline.

We have filed a registration statement covering the resale of 13,934,427 shares of our common stock that we sold to purchasers in a private placement and have agreed to keep such registration statement effective until the earliest of (i) the date on which the securities may be resold by the purchasers without registration and without regard to any volume or manner-of-sale limitations by reason of Rule 144, without the requirement for the Company to be in compliance with the current public information under Rule 144 under the Securities Act or any other rule of similar effect, (ii) the date on which all of the securities have been sold pursuant to such registration statement or Rule 144 under the Securities Act or any other rule of similar effect and (iii) the date that is one year following the date of effectiveness of the registration statement.

In addition, we have filed registration statements registering all shares of common stock that we may issue under our equity compensation plans or pursuant to equity awards made to newly hired employees outside of equity compensation plans. These shares can be freely sold in the public market upon issuance, subject to volume limitations applicable to affiliates.

Our management may invest or spend the proceeds of this offering in ways with which you may not agree or in ways that may not yield a return.

Our management will have broad discretion in the application of the net proceeds from this offering and could spend the proceeds in ways that do not improve our results of operations or enhance the value of our common stock. The failure by our management to apply these funds effectively could result in financial losses that could cause the price of our common stock to decline and delay the development of our product candidates. Pending their use, we may invest the net proceeds from this offering in a manner that does not produce income or that loses value.

In addition, the issuance from time to time of shares of our common stock in this offering, or our ability to issue these shares of common stock in this offering, could result in resales of our common stock by our current stockholders concerned about the potential dilution of their holdings. In turn, these resales could have the effect of depressing the market price for our common stock.

Purchasers will experience immediate dilution in the book value per share of the common stock purchased in the offering.

The price of our common stock to be sold in this offering is substantially higher than the net tangible book value per share of our common stock. Therefore, if you purchase shares of our common stock in this offering, you will pay

a price per share that substantially exceeds our net tangible book value per share after this offering. After giving effect to the sale of shares of our common stock in the aggregate amount of $100 million, and after deducting underwriting discounts and commissions and estimated offering expenses payable by us, our as adjusted net tangible book value as of September 30, 2022 would have been approximately $ million, or approximately $ per share. This represents an immediate increase in as adjusted net tangible book value of approximately $ per share to our existing stockholders and an immediate dilution in as adjusted net tangible book value of approximately $ per share to purchasers of our common stock in this offering. See "Dilution" in this prospectus supplement for more information.

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

The trading price of our common stock has been, and is likely to continue to be, volatile and could be subject to wide fluctuations in response to various factors, some of which are beyond our control. During the period from November 5, 2021 to February 28, 2023, the closing price of our common stock ranged from a high of $42.56 per share to a low of $8.57 per share. The stock market in general and the market for smaller biopharmaceutical companies in particular have experienced extreme volatility that has often been unrelated to the operating performance of particular companies.

You may experience future dilution as a result of future equity offerings.

In order to raise additional capital, we may in the future offer additional shares of our common stock or other securities convertible into or exchangeable for our common stock at prices that may not be the same as the price per share in this offering. We may sell shares or other securities in any other offering at a price per share that is less than the price per share paid by any investors in this offering, and investors purchasing shares or other securities in the future could have rights superior to existing stockholders. The price per share at which we sell additional shares of our common stock, or securities convertible or exchangeable into common stock, in future transactions may be higher or lower than the price per share paid by any investors in this offering.

We do not anticipate paying any cash dividends on our common stock in the foreseeable future. Accordingly, stockholders must rely on capital appreciation, if any, for any return on their investment.

We have never declared or paid cash dividends on our common stock. We currently intend to retain all of our future earnings, if any, to finance the growth and development of our business. As a result, capital appreciation, if any, of our common stock will be our stockholders' sole source of gain for the foreseeable future.

CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS AND INDUSTRY DATA

This prospectus supplement, the accompanying base prospectus and the documents incorporated by reference in each of this prospectus supplement and the accompanying base prospectus include "forward-looking statements" within the meaning of Section 27A of the Securities Act of 1933, as amended, or the Securities Act, and Section 21E of the Securities Exchange Act of 1934, as amended, or the Exchange Act. All statements, other than statements of historical fact, contained or incorporated by reference in this prospectus supplement and the accompanying base prospectus, including statements regarding our strategy, future operations, future financial position, future revenue, projected costs, prospects, plans and objectives of management, are forward-looking statements. The words "anticipate," "believe," "estimate," "expect," "intend," "may," "might," "plan," "predict," "project," "target," "potential," "would," "could," "should," "continue" and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words.

The forward-looking statements in this prospectus supplement, the accompanying prospectus and the information incorporated by reference herein and therein include, among other things, statements about:

- our business and operations following the separation and any benefits or costs of the separation, including the tax treatment of the separation;
- our post-separation relationships with bluebird bio, Inc., or bluebird bio, third parties, collaborators and our employees;
- our and Bristol Myers' Squibb's (BMS) plans for the continued commercialization of *Abecma* and the development and commercialization of earlier lines of therapy;
- our ability to operate as a stand-alone company and execute our strategic priorities;
- our ability to finance our operations and business initiatives and obtain funding for such activities;
- the timing, investment and associated activities involved in developing, obtaining regulatory approval for, launching, and commercializing our product candidates;
- our plans with respect to the development, manufacture or sale of our product candidates and the associated timing thereof, including the design and results of pre-clinical and clinical studies;
- the operational capabilities and timelines with respect to our in-house manufacturing facility;
- the safety profile and related adverse events of our product candidates;
- the perceived therapeutic benefits of our product candidates and the potential indications and market opportunities therefor;
- U.S. and foreign regulatory requirements for our product candidates, including any post-approval development and regulatory requirements, and the ability of our product candidates to meet such requirements;
- our ability to attract and retain key employees needed to execute our business plans and strategies and our expectations regarding our ability to manage the impact of any loss of key employees;
- our ability to obtain and maintain intellectual property protection for our product candidates and the strength thereof;
- our future financial performance, including estimates of our future revenues, expenses, cash flows, profitability, tax obligations, capital requirements and our needs for additional financing, liquidity sources, real estate need and concentration of voting control, as well as the timing and drivers thereof, and internal control over financial reporting;

- our ability to compete with other companies that are or may be developing or selling products that are competitive with our product candidates;
- the status of government regulation in the life sciences industry, particularly with respect to healthcare reform;
- the potential benefits of strategic collaboration agreements;
- potential indemnification liabilities we may owe to bluebird bio after the separation;
- the tax treatment of the distribution and limitations imposed on 2seventy bio under the tax matters agreement that 2seventy bio entered with bluebird bio in connection with the separation and distribution;
- the impact of rising inflation rates on our business, financial condition and results of operation;
- the fluctuation of the market price of our shares;
- trends and challenges in our current and potential markets; and
- other risks and uncertainties, including those listed under the section titled “Risk Factors.”

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 we make. We have included important factors in the cautionary statements included, or incorporated by reference, in this prospectus supplement, particularly in the “Risk Factors” section, that we believe could cause actual results or events to differ materially from the forward- looking statements that we make. You should also carefully review the risk factors and cautionary statements described in the other documents we file from time to time with the SEC, specifically our most recent Annual Report on Form 10-K, our Quarterly Reports on Form 10-Q and our Current Reports on Form 8-K. Our forward-looking statements do not reflect the potential impact of any future acquisitions, mergers, dispositions, joint ventures or investments we may make.

You should read this prospectus supplement, the accompanying base prospectus, the documents incorporated by reference in this prospectus supplement and the documents that we have filed as exhibits to the registration statement of which this prospectus supplement is a part completely and with the understanding that our actual future results may be materially different from what we expect. The forward-looking statements contained in this prospectus supplement and the accompanying base prospectus and incorporated by reference herein are made as of the date hereof, and we do not assume any obligation to update any forward-looking statements except as required by applicable law. Subsequent events and developments will impact matters implied by these forward-looking statements.

This prospectus supplement includes or incorporates by reference certain statistical and other industry and market data that we obtained from industry publications and research, surveys and studies conducted by third parties as well as our own estimates of potential market opportunities. Industry publications and third-party research, surveys and studies generally indicate that their information has been obtained from sources believed to be reliable, although they do not guarantee the accuracy or completeness of such information. Our estimates of the potential market opportunities for our product candidates include several key assumptions based on our industry knowledge, industry publications, third-party research and other surveys, which may be based on a small sample size and may fail to accurately reflect market opportunities. While we believe that our internal assumptions are reasonable, no independent source has verified such assumptions.

USE OF PROCEEDS

We estimate that the net proceeds to us from this offering will be approximately $ million, or approximately $ million if the underwriters exercise their option to purchase additional shares in full.

We currently intend to use the net proceeds from this offering, together with our existing cash, cash equivalents and marketable securities for research and development and clinical development costs to support the advancement of our product candidates and the expansion of our research and development programs; advancement of the KarMMa trials to support the use of *Abecma* in earlier lines of therapy, pursuant to our cost sharing arrangements with BMS; commercial activities in support of *Abecma*; working capital; capital expenditures; corporate development; and other general corporate purposes.

As of December 31, 2022, we had cash, cash equivalents and marketable securities of $267.7 million. This expected use of net proceeds from this offering represents our intentions based upon our current plans and business conditions, which could change in the future as our plans and business conditions evolve. The amounts and timing of our actual use of the net proceeds may vary significantly depending on numerous factors, including the actual net proceeds from this offering, the progress of our development, the status of and results from clinical trials, the timing of regulatory submissions and the outcome of regulatory review, as well as any collaborations that we may enter into with third parties for our product candidates, and any unforeseen cash needs. As a result, our management will retain broad discretion over the allocation of the net proceeds from this offering.

Pending the use of proceeds described above, we intend to invest the net proceeds in a variety of capital preservation investments, including short-term, investment-grade, interest-bearing instruments and U.S. government securities. We have not determined the amount of net proceeds to be used specifically for such purposes.

DILUTION

If you invest in our common stock in this offering, your ownership interest will be diluted immediately to the extent of the difference between the public offering price per share of our common stock you will pay in this offering and the as adjusted net tangible book value per share of our common stock immediately after this offering.

Our historical net tangible book value as of September 30, 2022 was approximately $303.6 million, or $8.01 per share of our common stock. Our historical net tangible book value is the amount of our total tangible assets less our total liabilities. Historical net tangible book value per share represents historical net tangible book value divided by the 37,912,215 shares of our common stock outstanding as of September 30, 2022.

After giving effect to the assumed issuance and sale of $100 million shares of our common stock at the public offering price of $ per share, and after deducting the underwriting discounts and commissions and estimated offering expenses payable by us, our as adjusted net tangible book value at September 30, 2022 would have been approximately $ million, or $ per share. This represents an immediate increase in as adjusted net tangible book value of $ per share to existing stockholders and an immediate dilution of $ per share to investors participating in this offering. Dilution per share to new investors is determined by subtracting as adjusted net tangible book value per share after this offering from the public offering price per share paid by new investors. The following table illustrates this per share dilution.

Public offering price per share		$
Historical net tangible book value per share as of September 30, 2022	$	
Increase in net tangible book value per share attributable to this offering	$	
As adjusted net tangible book value per share after giving effect to this offering	$	
Dilution per share to new investors purchasing shares in this offering		$

If the underwriters exercise their option to purchase an assumed $15 million additional shares in full, the immediate dilution in as adjusted net tangible book value per share to investors in this offering would be $ per share.

The table and discussion above are based on 37,912,215 shares of our common stock outstanding as of September 30, 2022, and exclude:

- 2,606,833 shares of common stock issuable upon exercise of options outstanding under our 2021 Stock Option and Incentive Plan at a weighted-average exercise price of $69.72 per share as of September 30, 2022;
- 1,331,817 shares of common stock issuable upon vesting and settlement of restricted stock units under our 2021 Stock Option and Incentive Plan as of September 30, 2022;
- 757,575 shares of common stock issuable upon the exercise of pre-funded warrants to purchase shares of common stock at an exercise price of $0.0001 per share outstanding as of September 30, 2022;
- 1,575,806 shares of common stock reserved for future issuance under our 2021 Stock Option and Incentive Plan as of September 30, 2022; and
- 200,625 shares of common stock reserved for future issuance under our 2021 Employee Stock Purchase Plan as of September 30, 2022.

To the extent that outstanding stock options are exercised, new stock options are issued, or we issue additional shares of common stock in the future, including pursuant to our sales agreement with Cowen and Company, LLC there will be further dilution to investors purchasing shares of common stock in this offering.

MATERIAL U.S. FEDERAL INCOME TAX CONSIDERATIONS FOR U.S. HOLDERS OF COMMON STOCK

The following is a discussion of certain material U.S. federal income tax consequences of the acquisition, ownership and disposition of our shares of common stock. This discussion applies only to shares of common stock that are held as capital assets for U.S. federal income tax purposes and is applicable only to holders who are receiving our shares of common stock in this offering.

This discussion is a summary only and does not describe all of the tax consequences that may be relevant to you in light of your particular circumstances, including but not limited to the alternative minimum tax, the Medicare tax on certain investment income and the different consequences (such as the effects of Section 451 of the Code) that may apply if you are subject to special rules that apply to certain types of investors, including but not limited to:

- financial institutions or financial services entities;
- broker-dealers;
- governments or agencies or instrumentalities thereof;
- regulated investment companies;
- real estate investment trusts;
- expatriates or former long-term residents of the U.S.;
- persons that actually or constructively own five percent or more of our voting shares;
- insurance companies;
- dealers or traders subject to a mark-to-market method of accounting with respect to the common stock;
- persons holding the common stock as part of a “straddle,” hedge, integrated transaction or similar transaction;
- U.S. holders (as defined below) whose functional currency is not the U.S. dollar;
- partnerships or other pass-through entities for U.S. federal income tax purposes and any beneficial owners of such entities; and
- tax-exempt entities.

This discussion is based on the Code, and administrative pronouncements, judicial decisions and final, temporary and proposed Treasury regulations as of the date hereof, which are subject to change, possibly on a retroactive basis, and changes to any of which subsequent to the date of this prospectus supplement may affect the tax consequences described herein. This discussion does not address any aspect of state, local or non-U.S. taxation, or any U.S. federal taxes other than income taxes (such as gift and estate taxes).

We have not sought, and will not seek, a ruling from the IRS as to any U.S. federal income tax consequence described herein. The IRS may disagree with the discussion herein, and its determination may be upheld by a court. Moreover, there can be no assurance that future legislation, regulations, administrative rulings or court decisions will not adversely affect the accuracy of the statements in this discussion. You are urged to consult your tax advisor with respect to the application of U.S. federal tax laws to your particular situation, as well as any tax consequences arising under the laws of any state, local or foreign jurisdiction.

This discussion does not consider the tax treatment of partnerships or other pass-through entities or persons who hold our common stock through such entities. If a partnership (or other entity or arrangement classified as a partnership or other pass-through entity for United States federal income tax purposes) is the beneficial owner of our common stock, the United States federal income tax treatment of a partner or member in the partnership or other

pass-through entity generally will depend on the status of the partner or member and the activities of the partnership or other pass-through entity. If you are a partner or member of a partnership or other pass-through entity holding our common stock, we urge you to consult your own tax advisor.

THIS DISCUSSION IS ONLY A SUMMARY OF CERTAIN UNITED STATES FEDERAL INCOME TAX CONSIDERATIONS ASSOCIATED WITH THE ACQUISITION, OWNERSHIP AND DISPOSITION OF OUR COMMON STOCK. EACH PROSPECTIVE INVESTOR IN OUR COMMON STOCK IS URGED TO CONSULT ITS OWN TAX ADVISOR WITH RESPECT TO THE PARTICULAR TAX CONSEQUENCES TO SUCH INVESTOR OF THE ACQUISITION, OWNERSHIP AND DISPOSITION OF OUR COMMON STOCK, INCLUDING THE APPLICABILITY AND EFFECT OF ANY UNITED STATES FEDERAL NON-INCOME, STATE, LOCAL, AND NON-U.S. TAX LAWS.

U.S. holders

This section applies to you if you are a "U.S. holder." A U.S. holder is a beneficial owner of our shares of common stock who or that is, for U.S. federal income tax purposes:

- an individual who is a citizen or resident of the United States;
- a corporation (or other entity taxable as a corporation) organized in or under the laws of the United States, any state thereof or the District of Columbia;
- an estate the income of which is includible in gross income for U.S. federal income tax purposes regardless of its source; or
- a trust, if (i) a court within the United States is able to exercise primary supervision over the administration of the trust and one or more U.S. persons (as defined in the Code) have authority to control all substantial decisions of the trust or (ii) it has a valid election in effect under Treasury Regulations to be treated as a U.S. person.

Taxation of Distributions. If we pay distributions in cash or other property (other than certain distributions of our stock or rights to acquire our stock) to U.S. holders of shares of our common stock, such distributions generally will constitute dividends for U.S. federal income tax purposes to the extent paid from our current or accumulated earnings and profits, as determined under U.S. federal income tax principles. Distributions in excess of current and accumulated earnings and profits will constitute a return of capital that will be applied against and reduce (but not below zero) the U.S. holder's adjusted tax basis in our common stock. Any remaining excess will be treated as gain realized on the sale or other disposition of the common stock and will be treated as described under "U.S. Holders—Gain or Loss on Sale, Taxable Exchange or Other Taxable Disposition of common stock" below.

Dividends we pay to a U.S. holder that is a taxable corporation generally will qualify for the dividends received deduction if the requisite holding period is satisfied. With certain exceptions (including, but not limited to, dividends treated as investment income for purposes of investment interest deduction limitations), and provided certain holding period requirements are met, dividends we pay to a non-corporate U.S. holder may constitute "qualified dividends" that will be subject to tax at the maximum tax rate accorded to long-term capital gains. If the holding period requirements are not satisfied, then a corporation may not be able to qualify for the dividends received deduction and would have taxable income equal to the entire dividend amount, and non-corporate holders may be subject to tax on such dividend at regular ordinary income tax rates instead of the preferential rate that applies to qualified dividend income.

Gain or Loss on Sale, Taxable Exchange or Other Taxable Disposition of common stock. Upon a sale or other taxable disposition of our common stock, a U.S. holder generally will recognize capital gain or loss in an amount equal to the difference between the amount realized and the U.S. holder's adjusted tax basis in the common stock. Any such capital gain or loss generally will be long-term capital gain or loss if the U.S. holder's holding period for the common stock so disposed of exceeds one year. If the holding period requirements are not satisfied, any gain on a sale or taxable disposition of the shares would be subject to short-term capital gain treatment and would be taxed at

regular ordinary income tax rates. Long-term capital gains recognized by non-corporate U.S. holders will be eligible to be taxed at reduced rates. The deductibility of capital losses is subject to limitations.

Generally, the amount of gain or loss recognized by a U.S. holder is an amount equal to the difference between (i) the sum of the amount of cash and the fair market value of any property received in such disposition and (ii) the U.S. holder's adjusted tax basis in its common stock so disposed of. A U.S. holder's adjusted tax basis in its common stock generally will equal the U.S. holder's acquisition cost for the common stock or less, in the case of a share of common stock, any prior distributions treated as a return of capital. In the case of any shares of common stock originally acquired as part of an investment unit, the acquisition cost for the share of common stock that were part of such unit would equal an allocable portion of the acquisition cost of the unit based on the relative fair market values of the components of the unit at the time of acquisition.

Information Reporting and Backup Withholding. In general, information reporting requirements may apply to dividends paid to a U.S. holder and to the proceeds of the sale or other disposition of our shares of common stock, unless the U.S. holder is an exempt recipient. Backup withholding may apply to such payments if the U.S. holder fails to provide a taxpayer identification number, a certification of exempt status or has been notified by the IRS that it is subject to backup withholding (and such notification has not been withdrawn).

Any amounts withheld under the backup withholding rules generally should be allowed as a refund or a credit against a U.S. holder's U.S. federal income tax liability provided the required information is timely furnished to the IRS.

Non-U.S. holders

This section applies to you if you are a "Non-U.S. holder." As used herein, the term "Non-U.S. holder" means a beneficial owner of our common stock who or that is for U.S. federal income tax purposes:

- a non-resident alien individual (other than certain former citizens and residents of the U.S. subject to U.S. tax as expatriates);
- a foreign corporation or
- an estate or trust that is not a U.S. holder;

but generally does not include an individual who is present in the U.S. for 183 days or more in the taxable year of disposition. If you are such an individual, you should consult your tax advisor regarding the U.S. federal income tax consequences of the acquisition, ownership or sale or other disposition of our common stock.

Taxation of Distributions. In general, any distributions we make to a Non-U.S. holder of shares of our common stock, to the extent paid out of our current or accumulated earnings and profits (as determined under U.S. federal income tax principles), will constitute dividends for U.S. federal income tax purposes and, provided such dividends are not effectively connected with the Non-U.S. holder's conduct of a trade or business within the United States, we will be required to withhold tax from the gross amount of the dividend at a rate of 30%, unless such Non-U.S. holder is eligible for a reduced rate of withholding tax under an applicable income tax treaty and provides proper certification of its eligibility for such reduced rate (usually on an IRS Form W-8BEN or W-8BEN-E). Any distribution not constituting a dividend will be treated first as reducing (but not below zero) the Non-U.S. holder's adjusted tax basis in its shares of our common stock and, to the extent such distribution exceeds the Non-U.S. holder's adjusted tax basis, as gain realized from the sale or other disposition of the common stock, which will be treated as described under "Non-U.S. Holders—Gain on Sale, Taxable Exchange or Other Taxable Disposition of common stock" below.

The withholding tax does not apply to dividends paid to a Non-U.S. holder who provides a Form W-8ECI, certifying that the dividends are effectively connected with the Non-U.S. holder's conduct of a trade or business within the United States. Instead, the effectively connected dividends will be subject to regular U.S. income tax as if the Non-U.S. holder were a U.S. resident, subject to an applicable income tax treaty providing otherwise. A Non-

U.S. corporation receiving effectively connected dividends may also be subject to an additional "branch profits tax" imposed at a rate of 30% (or a lower treaty rate).

Gain on Sale, Taxable Exchange or Other Taxable Disposition of common stock. A Non-U.S. holder generally will not be subject to U.S. federal income or withholding tax in respect of gain recognized on a sale, taxable exchange or other taxable disposition of our common stock, unless:

- the gain is effectively connected with the conduct of a trade or business by the Non-U.S. holder within the United States (and, under certain income tax treaties, is attributable to a United States permanent establishment or fixed base maintained by the Non-U.S. holder); or
- we are or have been a "U.S. real property holding corporation" for U.S. federal income tax purposes at any time during the shorter of the five-year period ending on the date of disposition or the period that the Non-U.S. holder held our common stock, and, in the case where shares of our common stock are regularly traded on an established securities market, the Non-U.S. holder has owned, directly or constructively, more than 5% of our common stock at any time within the shorter of the five-year period preceding the disposition or such Non-U.S. holder's holding period for the shares of our common stock. There can be no assurance that our common stock will be treated as regularly traded on an established securities market for this purpose.

Unless an applicable treaty provides otherwise, gain described in the first bullet point above will be subject to tax at generally applicable U.S. federal income tax rates as if the Non-U.S. holder were a U.S. resident. Any gains described in the first bullet point above of a Non-U.S. holder that is a foreign corporation may also be subject to an additional "branch profits tax" at a 30% rate (or lower treaty rate).

If the second bullet point above applies to a Non-U.S. holder, gain recognized by such holder on the sale, exchange or other disposition of shares of our common stock will be subject to tax at generally applicable U.S. federal income tax rates, and a buyer of such shares may be required to withhold U.S. federal income tax at a rate of 15% of the amount realized upon the disposition. We expect not to be classified as a "U.S. real property holding corporation" for U.S. federal income tax purposes. However, such determination is factual in nature and subject to change and no assurance can be provided as to whether we will be a "U.S. real property holding corporation" for U.S. federal income tax purposes in the future.

Information Reporting and Backup Withholding. Information returns will be filed with the IRS in connection with payments of dividends and the proceeds from a sale or other disposition of our shares of common stock. A Non-U.S. holder may have to comply with certification procedures to establish that it is not a United States person in order to avoid information reporting and backup withholding requirements. The certification procedures required to claim a reduced rate of withholding under a treaty will generally satisfy the certification requirements necessary to avoid the backup withholding as well. The amount of any backup withholding from a payment to a Non-U.S. holder will be allowed as a credit against such holder's U.S. federal income tax liability and may entitle such holder to a refund, provided that the required information is timely furnished to the IRS.

FATCA Withholding Taxes. Sections 1471 through 1474 of the Code and the Treasury Regulations and administrative guidance promulgated thereunder (commonly referred as the "Foreign Account Tax Compliance Act" or "FATCA") generally impose withholding at a rate of 30% in certain circumstances on dividends in respect of, and (subject to the proposed Treasury Regulations discussed below) gross proceeds from the sale or other disposition of, securities (including shares of our common stock) which are held by or through certain foreign financial institutions (including investment funds), unless any such institution (i) enters into, and complies with, an agreement with the IRS to report, on an annual basis, information with respect to interests in, and accounts maintained by, the institution that are owned by certain U.S. persons and by certain non-U.S. entities that are wholly or partially owned by U.S. persons and to withhold on certain payments, or (ii) if required under an intergovernmental agreement between the United States and an applicable foreign country, reports such information to its local tax authority, which will exchange such information with the U.S. authorities. An intergovernmental agreement between the United States and an applicable foreign country may modify these requirements. Accordingly, the entity through which shares of our common stock are held will affect the determination of whether such withholding is required. Similarly, dividends in respect of, and (subject to the proposed Treasury Regulations discussed below) gross proceeds from the

sale or other disposition of, our common stock held by an investor that is a non-financial non-U.S. entity that does not qualify under certain exceptions will generally be subject to withholding at a rate of 30%, unless such entity either (i) certifies to the applicable withholding agent that such entity does not have any "substantial United States owners" or (ii) provides certain information regarding the entity's "substantial United States owners," which will in turn be provided to the U.S. Department of Treasury.

Under the applicable Treasury Regulations and administrative guidance, withholding under FATCA generally applies to payments of dividends in respect of our common stock. While withholding under FATCA generally would also apply to payments of gross proceeds from the sale or other disposition of securities (including shares of our common stock), proposed Treasury Regulations eliminate FATCA withholding on payments of gross proceeds entirely. Taxpayers generally may rely on these proposed Treasury Regulations until final Treasury Regulations are issued. All holders should consult their tax advisors regarding the possible implications of FATCA on their investment in shares of our common stock.

UNDERWRITING

The Company and the underwriters named below have entered into an underwriting agreement with respect to the shares being offered. Subject to certain conditions, each underwriter has severally agreed to purchase the number of shares indicated in the following table. Goldman Sachs & Co. LLC, Cowen and Company, LLC and SVB Securities LLC are the representatives of the underwriters.

Underwriters	Number of Shares
Goldman Sachs & Co. LLC	
Cowen and Company, LLC	
SVB Securities LLC	
Total	

The underwriters are committed to take and pay for all of the shares being offered, if any are taken, other than the shares covered by the option described below unless and until this option is exercised.

The underwriters have an option to buy up to an additional shares from the company to cover sales by the underwriters of a greater number of shares than the total number set forth in the table above. They may exercise that option for 30 days. If any shares are purchased pursuant to this option, the underwriters will severally purchase shares in approximately the same proportion as set forth in the table above.

The following table shows the per share and total underwriting discounts and commissions to be paid to the underwriters by the company. Such amounts are shown assuming both no exercise and full exercise of the underwriters' option to purchase additional shares.

Paid by the Company	No Exercise	Full Exercise
Per Share	$	$
Total	$	$

Shares sold by the underwriters to the public will initially be offered at the initial public offering price set forth on the cover of this prospectus. Any shares sold by the underwriters to securities dealers may be sold at a discount of up to $ per share from the initial public offering price. After the initial offering of the shares, the representatives may change the offering price and the other selling terms. The offering of the shares by the underwriters is subject to receipt and acceptance and subject to the underwriters' right to reject any order in whole or in part.

The Company and its officers and directors have agreed with the underwriters, subject to certain exceptions, not to dispose of or hedge any of their common stock or securities convertible into or exchangeable for shares of common stock during the period from the date of this prospectus supplement continuing through the date 90 days after the date of this prospectus supplement, except with the prior written consent of the representatives. This agreement does not apply to any existing employee benefit plans.

The restrictions described in the immediately preceding paragraph do not apply, subject in certain cases to various conditions, to our directors, officers, or equity holders with respect to:

(i) transactions relating to shares acquired in this offering or in transactions relating to shares acquired in open market transactions after the date of this prospectus, provided, that no filing under Section 16(a) of the Exchange Act, or any other public disclosure shall be required or shall be made during the Lock-Up Period in connection with subsequent sales of shares acquired in this offering or in such open market transactions,

(ii) transfers of shares or derivative securities as a bona fide gift or gifts, provided, that the donee or donees thereof agree to be bound in writing by the restrictions set forth herein, and provided, further, that no filing under Section 16(a) of the Exchange Act or other public disclosure shall be required or shall be made during the Lock-Up Period,

(iii) transfers of shares or derivative securities to any immediate family member of the undersigned or any trust or limited family partnership for the direct or indirect benefit of the party to the lock-up agreement or the immediate family of the party to the lock-up agreement, provided, that the trustee of the trust agrees to be bound in writing by the restrictions set forth in such lock-up agreement, and provided, further, that any such transfer shall not involve a disposition for value, provided, further, that no filing under Section 16(a) of the Exchange Act or other public filing, report or announcement by or on behalf of the party to the lock-up agreement reporting a reduction in beneficial ownership of shares shall be required or shall be voluntarily made during the Lock-Up Period (other than any required Form 5 filing after the end of the calendar year in which such transaction occurs),

(iv) transfers of shares or derivative securities by will, other testamentary document or intestate succession to the legal representative, heir, beneficiary or a member of the immediate family of the party to the lock-up agreement in a transaction not involving a disposition for value, provided, that the transferee thereof agrees to be bound in writing by the restrictions set in such lock-up agreement, and provided, further, that no filing under Section 16(a) of the Exchange Act or other public filing, report or announcement by or on behalf of the party to the lock-up agreement reporting a reduction in beneficial ownership of shares shall be required or shall be made during the Lock-Up Period except for a filing under Section 16(a) of the Exchange Act that indicates by footnote disclosure or otherwise the nature of the transfer,

(v) transfers of shares pursuant to a trading plan established pursuant to Rule 10b5-1 under the Exchange Act prior to the date of the relevant lock-up agreement, which trading plan shall not be amended during the Lock-Up Period but may be terminated during the Lock-Up Period,

(vi) the establishment of a trading plan pursuant to Rule 10b5-1 under the Exchange Act providing for the transfer of shares, to the extent that such plan does not provide for the transfer of shares during the Lock-Up Period; or

(vii) transactions made with the prior written consent of Goldman Sachs & Co. LLC, Cowen and Company, LLC and SVB Securities LLC on behalf of the underwriters.

In addition, notwithstanding the foregoing, if the party to a lock-up agreement is a corporation, the corporation may transfer the capital stock of the Company to any wholly-owned subsidiary of such corporation; provided, however, that in any such case, it shall be a condition to the transfer that the transferee execute an agreement stating that the transferee is receiving and holding such capital stock subject to the provisions of the relevant lock-up agreement and there shall be no further transfer of such capital stock except in accordance with the relevant lock-up agreement, and provided, further, that any such transfer shall not involve a disposition for value.

Furthermore, the restrictions described above will not be deemed to restrict or prohibit the exercise of any option, warrant or other right to acquire shares, the settlement of any share-settled share appreciation rights, restricted shares or restricted share units or the conversion of any convertible security into shares, in each case pursuant to an equity plan of the Company described herein, provided that the shares or other securities remain subject to the lock-up agreement and (b) the party to the lock-up agreement may transfer or sell such number of shares as is necessary solely to satisfy any tax withholding obligations incurred upon the vesting of any restricted stock units that vest during the Lock-Up Period, through the surrender to the Company of shares or through sales of shares in the market, provided, that any shares received by the party to the lock-up agreement upon such vesting shall be subject to the restrictions provided for in the relevant lock-up agreement, provided, further, that any related filing under Section 16(a) of the Exchange Act must note that such transfer or sale was made solely to satisfy tax withholding obligations and no other public filing, report or announcement by or on behalf of the party to the lockup agreement reporting a reduction in beneficial ownership of shares shall be required or shall be made during the Lock-Up Period.

In connection with the offering, the underwriters may purchase and sell shares of common stock in the open market. These transactions may include short sales, stabilizing transactions and purchases to cover positions created by short sales. Short sales involve the sale by the underwriters of a greater number of shares than they are required to purchase in the offering, and a short position represents the amount of such sales that have not been covered by

subsequent purchases. A “covered short position” is a short position that is not greater than the amount of additional shares for which the underwriters’ option described above may be exercised. The underwriters may cover any covered short position by either exercising their option to purchase additional shares or purchasing shares in the open market. In determining the source of shares to cover the covered short position, the underwriters will consider, among other things, the price of shares available for purchase in the open market as compared to the price at which they may purchase additional shares pursuant to the option described above. “Naked” short sales are any short sales that create a short position greater than the amount of additional shares for which the option described above may be exercised. The underwriters must cover any such naked short position by purchasing shares in the open market. A naked short position is more likely to be created if the underwriters are concerned that there may be downward pressure on the price of the common stock in the open market after pricing that could adversely affect investors who purchase in the offering. Stabilizing transactions consist of various bids for or purchases of common stock made by the underwriters in the open market prior to the completion of the offering.

The underwriters may also impose a penalty bid. This occurs when a particular underwriter repays to the underwriters a portion of the underwriting discount received by it because the representatives have repurchased shares sold by or for the account of such underwriter in stabilizing or short covering transactions.

Purchases to cover a short position and stabilizing transactions, as well as other purchases by the underwriters for their own accounts, may have the effect of preventing or retarding a decline in the market price of the company’s stock, and together with the imposition of the penalty bid, may stabilize, maintain or otherwise affect the market price of the common stock. As a result, the price of the common stock may be higher than the price that otherwise might exist in the open market. The underwriters are not required to engage in these activities and may end any of these activities at any time. These transactions may be effected on the Nasdaq Global Select Market, in the over-the-counter market or otherwise.

European Economic Area

In relation to each EEA Member State (each a “Relevant Member State”), no common shares (the “Shares”) have been offered or will be offered pursuant to the Offering to the public in that Relevant Member State prior to the publication of a prospectus in relation to the Shares which has been approved by the competent authority in that Relevant Member State or, where appropriate, approved in another Relevant Member State and notified to the competent authority in that Relevant Member State, all in accordance with the Prospectus Regulation, except that the Shares may be offered to the public in that Relevant Member State at any time:

a. to any legal entity which is a qualified investor as defined under Article 2 of the Prospectus Regulation;

b. to fewer than 150 natural or legal persons (other than qualified investors as defined under Article 2 of the Prospectus Regulation) subject to obtaining the prior consent of the Joint Global Coordinators for any such offer; or

c. in any other circumstances falling within Article 1(4) of the Prospectus Regulation,

provided that no such offer of the Shares shall require the Company and/or Selling Shareholders or any Bank to publish a prospectus pursuant to Article 3 of the Prospectus Regulation or supplement a prospectus pursuant to Article 23 of the Prospectus Regulation.

For the purposes of this provision, the expression an ‘offer to the public’ in relation to the Shares in any Relevant Member State means the communication in any form and by any means of sufficient information on the terms of the offer and any Shares to be offered so as to enable an investor to decide to purchase any Shares, and the expression "Prospectus Regulation" means Regulation (EU) 2017/1129.

Each person in a Relevant Member State who receives any communication in respect of, or who acquires any Shares under, the Offering contemplated hereby will be deemed to have represented, warranted and agreed to and with each of the Underwriters and their affiliates and the Company that:

a. it is a qualified investor within the meaning of the Prospectus Regulation; and

b. in the case of any Shares acquired by it as a financial intermediary, as that term is used in Article 5 of the Prospectus Regulation, (i) the Shares acquired by it in the Offering have not been acquired on a nondiscretionary basis on behalf of, nor have they been acquired with a view to their offer or resale to, persons in any Relevant Member State other than qualified investors, as that term is defined in the Prospectus Regulation, or have been acquired in other circumstances falling within the points (a) to (d) of Article 1(4) of the Prospectus Regulation and the prior consent of the Joint Global Coordinators has been given to the offer or resale; or (ii) where the Shares have been acquired by it on behalf of persons in any Relevant Member State other than qualified investors, the offer of those Shares to it is not treated under the Prospectus Regulation as having been made to such persons.

The Company, the Underwriters and their affiliates, and others will rely upon the truth and accuracy of the foregoing representation, acknowledgement and agreement. Notwithstanding the above, a person who is not a qualified investor and who has notified the Joint Global Coordinators of such fact in writing may, with the prior consent of the Joint Global Coordinators, be permitted to acquire Shares in the Offering.

United Kingdom

This Prospectus and any other material in relation to the common shares (the “Shares”) described herein is only being distributed to, and is only directed at, and any investment or investment activity to which this Prospectus relates is available only to, and will be engaged in only with persons who are (i) persons having professional experience in matters relating to investments who fall within the definition of investment professionals in Article 19(5) of the (Financial Promotion) Order, or FPO; or (ii) high net worth entities falling within Article 49(2)(a) to (d) of the FPO; (iii) outside the UK; or (iv) persons to whom an invitation or inducement to engage in investment activity (within the meaning of Section 21 of the Financial Services and Markets Act, or FSMA) in connection with the issue or sale of any Shares may otherwise lawfully be communicated or caused to be communicated, (all such persons together being referred to as “Relevant Persons”). The Shares are only available in the UK to, and any invitation, offer or agreement to purchase or otherwise acquire the Shares will be engaged in only with, the Relevant Persons. This Prospectus and its contents are confidential and should not be distributed, published or reproduced (in whole or in part) or disclosed by recipients to any other person in the UK. Any person in the UK that is not a Relevant Person should not act or rely on this Prospectus or any of its contents.

No Shares have been offered or will be offered pursuant to the Offering to the public in the United Kingdom prior to the publication of a prospectus in relation to the Shares which has been approved by the Financial Conduct Authority, except that the Shares may be offered to the public in the United Kingdom at any time:

a. to any legal entity which is a qualified investor as defined under Article 2 of the UK Prospectus Regulation;

b. to fewer than 150 natural or legal persons (other than qualified investors as defined under Article 2 of the UK Prospectus Regulation), subject to obtaining the prior consent of the Global Coordinators for any such offer; or

c. in any other circumstances falling within Section 86 of the FSMA.

provided that no such offer of the Shares shall require the Company and/or any Underwriters or any of their affiliates to publish a prospectus pursuant to Section 85 of the FSMA or supplement a prospectus pursuant to Article 23 of the UK Prospectus Regulation. For the purposes of this provision, the expression an "offer to the public" in relation to the Shares in the United Kingdom means the communication in any form and by any means of sufficient information on the terms of the offer and any Shares to be offered so as to enable an investor to decide to purchase or subscribe for any Shares and the expression “UK Prospectus Regulation” means Regulation (EU) 2017/1129 as it forms part of domestic law by virtue of the European Union (Withdrawal) Act 2018.

Each person in the UK who acquires any Shares in the Offer or to whom any offer is made will be deemed to have represented, acknowledged and agreed to and with the Company, the Underwriters and their affiliates that it meets the criteria outlined in this section.

Canada

The securities may be sold in Canada only to purchasers purchasing, or deemed to be purchasing, as principal that are accredited investors, as defined in National Instrument 45-106 Prospectus Exemptions or subsection 73.3(1) of the Securities Act (Ontario), and are permitted clients, as defined in National Instrument 31-103 Registration Requirements, Exemptions, and Ongoing Registrant Obligations. Any resale of the securities must be made in accordance with an exemption form, or in a transaction not subject to, the prospectus requirements of applicable securities laws.

Securities legislation in certain provinces or territories of Canada may provide a purchaser with remedies for rescission or damages if this offering memorandum (including any amendment thereto) contains a misrepresentation, provided that the remedies for rescission or damages are exercised by the purchaser within the time limit prescribed by the securities legislation of the purchaser's province or territory. The purchaser should refer to any applicable provisions of the securities legislation of the purchaser's province or territory of these rights or consult with a legal advisor.

Pursuant to section 3A.3 of National Instrument 33-105 Underwriting Conflicts (NI 33-105), the underwriters are not required to comply with the disclosure requirements of NI 33-105 regarding underwriter conflicts of interest in connection with this offering.

Hong Kong

The shares may not be offered or sold in Hong Kong by means of any document other than (i) in circumstances which do not constitute an offer to the public within the meaning of the Companies (Winding Up and Miscellaneous Provisions) Ordinance (Cap. 32 of the Laws of Hong Kong) ("Companies (Winding Up and Miscellaneous Provisions) Ordinance") or which do not constitute an invitation to the public within the meaning of the Securities and Futures Ordinance (Cap. 571 of the Laws of Hong Kong) ("Securities and Futures Ordinance"), or (ii) to "professional investors" as defined in the Securities and Futures Ordinance and any rules made thereunder, or (iii) in other circumstances which do not result in the document being a "prospectus" as defined in the Companies (Winding Up and Miscellaneous Provisions) Ordinance, and no advertisement, invitation or document relating to the shares may be issued or may be in the possession of any person for the purpose of issue (in each case whether in Hong Kong or elsewhere), which is directed at, or the contents of which are likely to be accessed or read by, the public in Hong Kong (except if permitted to do so under the securities laws of Hong Kong) other than with respect to shares which are or are intended to be disposed of only to persons outside Hong Kong or only to "professional investors" in Hong Kong as defined in the Securities and Futures Ordinance and any rules made thereunder.

Singapore

This prospectus has not been registered as a prospectus with the Monetary Authority of Singapore. Accordingly, this prospectus and any other document or material in connection with the offer or sale, or invitation for subscription or purchase, of the shares may not be circulated or distributed, nor may the shares be offered or sold, or be made the subject of an invitation for subscription or purchase, whether directly or indirectly, to persons in Singapore other than (i) to an institutional investor (as defined under Section 4A of the Securities and Futures Act, Chapter 289 of Singapore (the "SFA")) under Section 274 of the SFA, (ii) to a relevant person (as defined in Section 275(2) of the SFA) pursuant to Section 275(1) of the SFA, or any person pursuant to Section 275(1A) of the SFA, and in accordance with the conditions specified in Section 275 of the SFA or (iii) otherwise pursuant to, and in accordance with the conditions of, any other applicable provision of the SFA, in each case subject to conditions set forth in the SFA.

Where the shares are subscribed or purchased under Section 275 of the SFA by a relevant person which is a corporation (which is not an accredited investor (as defined in Section 4A of the SFA)) the sole business of which is to hold investments and the entire share capital of which is owned by one or more individuals, each of whom is an accredited investor, the securities (as defined in Section 239(1) of the SFA) of that corporation shall not be transferable for 6 months after that corporation has acquired the shares under Section 275 of the SFA except: (1) to an institutional investor under Section 274 of the SFA or to a relevant person (as defined in Section 275(2) of the SFA), (2) where such transfer arises from an offer in that corporation's securities pursuant to Section 275(1A) of the

SFA, (3) where no consideration is or will be given for the transfer, (4) where the transfer is by operation of law, (5) as specified in Section 276(7) of the SFA, or (6) as specified in Regulation 32 of the Securities and Futures (Offers of Investments) (Shares and Debentures) Regulations 2005 of Singapore ("Regulation 32")

Where the shares are subscribed or purchased under Section 275 of the SFA by a relevant person which is a trust (where the trustee is not an accredited investor (as defined in Section 4A of the SFA)) whose sole purpose is to hold investments and each beneficiary of the trust is an accredited investor, the beneficiaries' rights and interest (howsoever described) in that trust shall not be transferable for 6 months after that trust has acquired the shares under Section 275 of the SFA except: (1) to an institutional investor under Section 274 of the SFA or to a relevant person (as defined in Section 275(2) of the SFA), (2) where such transfer arises from an offer that is made on terms that such rights or interest are acquired at a consideration of not less than S$200,000 (or its equivalent in a foreign currency) for each transaction (whether such amount is to be paid for in cash or by exchange of securities or other assets), (3) where no consideration is or will be given for the transfer, (4) where the transfer is by operation of law, (5) as specified in Section 276(7) of the SFA, or (6) as specified in Regulation 32.

Japan

The securities have not been and will not be registered under the Financial Instruments and Exchange Act of Japan (Act No. 25 of 1948, as amended), or the FIEA. The securities may not be offered or sold, directly or indirectly, in Japan or to or for the benefit of any resident of Japan (including any person resident in Japan or any corporation or other entity organized under the laws of Japan) or to others for reoffering or resale, directly or indirectly, in Japan or to or for the benefit of any resident of Japan, except pursuant to an exemption from the registration requirements of the FIEA and otherwise in compliance with any relevant laws and regulations of Japan.

The company estimates that its total expenses of the offering, excluding underwriting discounts and commissions, will be approximately $. We have agreed to reimburse the underwriters for expenses relating to the clearance of this offering with the Financial Industry Regulatory Authority, Inc. in an amount of up to $35,000.

The company has agreed to indemnify the several underwriters against certain liabilities, including liabilities under the Securities Act of 1933.

The underwriters and their respective affiliates are full service financial institutions engaged in various activities, which may include sales and trading, commercial and investment banking, advisory, investment management, investment research, principal investment, hedging, market making, brokerage and other financial and non-financial activities and services. Certain of the underwriters and their respective affiliates have provided, and may in the future provide, a variety of these services to the issuer and to persons and entities with relationships with the issuer, for which they received or will receive customary fees and expenses. In addition, we entered into an at-the-market offering program sales agreement with Cowen and Company, LLC on November 18, 2022, pursuant to which, we may offer and sell, from time to time at our discretion, shares of our common stock having an aggregate offering price of up to $150 million through Cowen and Company, LLC as our sales agent, for which Cowen and Company, LLC has received customary fees and expenses.

In the ordinary course of their various business activities, the underwriters and their respective affiliates, officers, directors and employees may purchase, sell or hold a broad array of investments and actively trade securities, derivatives, loans, commodities, currencies, credit default swaps and other financial instruments for their own account and for the accounts of their customers, and such investment and trading activities may involve or relate to assets, securities and/or instruments of the issuer (directly, as collateral securing other obligations or otherwise) and/or persons and entities with relationships with the issuer. The underwriters and their respective affiliates may also communicate independent investment recommendations, market color or trading ideas and/or publish or express independent research views in respect of such assets, securities or instruments and may at any time hold, or recommend to clients that they should acquire, long and/or short positions in such assets, securities and instruments.

LEGAL MATTERS

The validity of the shares of common stock offered hereby will be passed upon by Goodwin Procter LLP, Boston, Massachusetts. Ropes & Gray LLP is acting as counsel for the underwriters in connection with certain legal matters relating to this offering.

EXPERTS

Ernst & Young LLP, independent registered public accounting firm, has audited our consolidated and combined financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2021, as set forth in their report, which is incorporated by reference in this prospectus supplement and elsewhere in the registration statement. Our financial statements are incorporated by reference in reliance on Ernst & Young LLP's report, given on their authority as experts in accounting and auditing.

WHERE YOU CAN FIND MORE INFORMATION

We file annual, quarterly and current reports, proxy statements and other information with the SEC. Our SEC filings are available to the public over the Internet at the SEC's website at http:// www.sec.gov. Copies of certain information filed by us with the SEC are also available on our website at https://www.2seventybio.com/. Our website is not a part of this prospectus supplement and information contained on, or that can be accessed through our website, is not incorporated by reference in this prospectus supplement and the accompanying base prospectus.

This prospectus supplement is part of a registration statement we filed with the SEC. This prospectus supplement omits some information contained in the registration statement in accordance with SEC rules and regulations. You should review the information and exhibits in the registration statement for further information about us and our consolidated subsidiary and the securities we are offering. Statements in this prospectus supplement and the accompanying base prospectus concerning any document we filed as an exhibit to the registration statement or that we otherwise filed with the SEC are not intended to be comprehensive and are qualified by reference to these filings and the exhibits attached thereto. You should review the complete document to evaluate these statements. You can obtain a copy of the registration statement from the SEC's website.

INCORPORATION OF CERTAIN DOCUMENTS BY REFERENCE

The SEC allows us to incorporate by reference much of the information we file with the SEC, which means that we can disclose important information to you by referring you to those publicly available documents. The information that we incorporate by reference in this prospectus supplement and the accompanying base prospectus is considered to be part of this prospectus supplement. Because we are incorporating by reference future filings with the SEC, this prospectus supplement is continually updated and those future filings may modify or supersede some of the information included or incorporated in this prospectus supplement and the accompanying base prospectus. This means that you must look at all of the SEC filings that we incorporate by reference to determine if any of the statements in this prospectus supplement or in any document previously incorporated by reference have been modified or superseded. This prospectus supplement incorporates by reference the documents listed below and any future filings we make with the SEC under Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act (in each case, other than those documents or the portions of those documents not deemed to be filed) until the offering of the securities offered hereby is terminated or completed. We are not, however, incorporating by reference any documents or portions thereof, whether specifically listed below or filed in the future, that are not deemed "filed" with the SEC, including any information furnished pursuant to Items 2.02 or 7.01 of Form 8-K or related exhibits furnished pursuant to Item 9.01 of Form 8-K:

- Annual Report on Form 10-K for the year ended December 31, 2021 filed on March 22, 2022, including the information specifically incorporated by reference into our Annual Report on Form 10-K from our definitive proxy statement on Schedule 14A (other than information furnished rather than filed) filed on April 26, 2022;
- Quarterly Reports on Form 10-Q for the quarters ended March 31, 2022, June 30, 2022, and September 30, 2022, filed on May 12, 2022, August 10, 2022 and November 7, 2022, respectively;

- Current Reports on Form 8-K filed on January 6, 2022, January 11, 2022, March 16, 2022, April 8, 2022, April 29, 2022, June 3, 2022, June 13, 2022, August 10, 2022, September 7, 2022, October 27, 2022, November 3, 2022, November 18, 2022, January 5, 2023, January 6, 2023, January 9, 2023, February 6, 2023; February 10, 2023; February 23, 2023; and February 28, 2023 (in each case, except for information contained therein which is furnished rather than filed);

- The description of our common stock contained in the Information Statement filed with the SEC as Exhibit 99.1 to our Form 10, including any further amendments thereto or reports filed for the purposes of updating such description, including Exhibit 4.4 to our Annual Report on Form 10-K for the year ended December 31, 2021.

You may request a copy of these filings, at no cost, by writing or calling us at the following address or telephone number:

2seventy bio, Inc.
60 Binney Street
Cambridge, Massachusetts 02142
(339) 499-9300

PROSPECTUS

$400,000,000

Common Stock
Preferred Stock
Debt Securities
Warrants
Units

We may from time to time issue, in one or more series or classes, up to $400,000,000 in aggregate principal amount of our common stock, preferred stock, debt securities, warrants and/or units, in any combination, together or separately, in one or more offerings in amounts, at prices and on the terms that we will determine at the time of the offering and which will be set forth in a prospectus supplement to this prospectus and any related free writing prospectus.

We may offer these securities separately or together in units. Each time we sell securities described herein, we will provide prospective investors with a supplement to this prospectus that will specify the terms of the securities being offered. We may sell these securities to or through underwriters or dealers and also to other purchasers or through agents. We will set forth the names of any underwriters or agents, and any fees, conversions, or discount arrangements, in the applicable prospectus supplement. We may not sell any securities under this prospectus without delivery of the applicable prospectus supplement. You should read this document and any prospectus supplement or amendment carefully before you invest in our securities.

Our common stock is listed on The Nasdaq Global Select Market under the symbol "TSVT." On November 4, 2022, the closing price for our common stock, as reported on The Nasdaq Global Select Market, was $15.51 per share. Our principal executive offices are located at 60 Binney Street, Cambridge, Massachusetts 02142.

Investing in these securities involves certain risks. See "Risk Factors" on page 2 of this prospectus as well as those included in any accompanying prospectus supplement and in the documents incorporated by reference in this prospectus for a discussion of the factors you should carefully consider before deciding to purchase these securities.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or passed upon the adequacy or accuracy of this prospectus. Any representation to the contrary is a criminal offense.

The date of this prospectus is November 18, 2022

ABOUT THIS PROSPECTUS

This prospectus is part of a registration statement that we filed with the Securities and Exchange Commission (the "SEC") utilizing a "shelf" registration process. Under this shelf registration process, we may from time to time sell any combination of the securities described in this prospectus in one or more offerings for an aggregate initial offering price of up to $400,000,000.

This prospectus provides you with a general description of the securities we may offer. Each time we sell securities, we will provide one or more prospectus supplements that will contain specific information about the terms of the offering. The prospectus supplement may also add, update or change information contained in this prospectus. This prospectus, together with any accompanying prospectus supplement, contains important information you should know before investing in our securities, including important information about us and the securities being offered. You should read both this prospectus and the accompanying prospectus supplement together with the additional information described under the headings "Where You Can Find More Information" and "Incorporation by Reference" beginning on page 28 of this prospectus.

You should rely only on the information contained in or incorporated by reference in this prospectus, any accompanying prospectus supplement or in any related free writing prospectus filed by us with the SEC. We have not authorized anyone to provide you with different information. This prospectus and the accompanying prospectus supplement do not constitute an offer to sell or the solicitation of an offer to buy any securities other than the securities described in the accompanying prospectus supplement or an offer to sell or the solicitation of an offer to buy such securities in any circumstances in which such offer or solicitation is unlawful. You should assume that the information appearing in this prospectus, any prospectus supplement, the documents incorporated by reference and any related free writing prospectus is accurate only as of their respective dates. Our business, financial condition, results of operations and prospects may have changed materially since those dates. This prospectus, any applicable prospectus supplement and the information incorporated herein or therein by reference contains market data, industry statistics and other data that have been obtained or compiled from information made available by independent third parties. We have not independently verified the accuracy and completeness of such data.

THIS PROSPECTUS MAY NOT BE USED TO OFFER AND SELL SECURITIES UNLESS IT IS ACCOMPANIED BY AN ADDITIONAL PROSPECTUS OR A PROSPECTUS SUPPLEMENT.

For purposes of this prospectus, references to the terms "TSVT," "the Company," "we," "us" and "our" refer to 2seventy bio, Inc., together with its subsidiaries, unless the context otherwise requires.

We own various U.S. federal trademark applications and unregistered trademarks, including our company name. All other trademarks or trade names referred to in this prospectus are the property of their respective owners. Solely for convenience, the trademarks and trade names in this prospectus are referred to without the symbols ® and ™, but such references should not be construed as any indicator that their respective owners will not assert, to the fullest extent under applicable law, their rights thereto.

RISK FACTORS

Investing in our securities involves a high degree of risk. You should carefully consider the risks set forth in our filings with the SEC that are incorporated by reference herein and any prospectus supplement, as well as other information we include or incorporate by reference into this prospectus and any applicable prospectus supplement, before making an investment decision. Our business, financial condition or results of operations could be materially adversely affected by the materialization of any of these risks. The trading price of our securities could decline due to the materialization of any of these risks, and you may lose all or part of your investment. This prospectus and the documents incorporated herein by reference also contain forward-looking statements that involve risks and uncertainties. Actual results could differ materially from those anticipated in these forward-looking statements as a result of certain factors, including the risks described in the documents incorporated herein by reference, including our most recent Annual Report on Form 10-K, our Quarterly Reports on Form 10-Q and our Current Reports on Form 8-K and the other documents we file with the SEC that are deemed incorporated by reference into this prospectus.

SPECIAL NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus, including the documents that we incorporate by reference, includes forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended (the "Securities Act"), and Section 21E of the Securities Exchange Act of 1934, as amended (the "Exchange Act"). Forward-looking statements relate to, among others, our plans, objectives and expectations for our business, operations and financial performance and condition, and can be identified by terminology such as "may," "will," "could," "should," "expect," "intend," "plan," "anticipate," "believe," "estimate," "predict," "potential," "project," "seek," "endeavor," "target," "continue" and similar expressions that do not relate solely to historical matters. Forward-looking statements are based on management's belief and assumptions and on information currently available to management. Although we believe that the expectations reflected in forward-looking statements are reasonable, such statements involve known and unknown risks, uncertainties and other factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by forward-looking statements.

Forward-looking statements include, but are not limited to, statements about:

- our business and operations following the separation from bluebird bio and any benefits or costs of the separation, including the tax treatment;
- our post-separation relationships with bluebird bio, third parties, collaborators and our employees;
- our ability to operate as a stand-alone company and execute our strategic priorities;
- our ability to finance our operations and business initiatives and obtain funding for such activities;
- the timing, investment and associated activities involved in developing, obtaining regulatory approval for, launching, and commercializing our product candidates;
- our plans with respect to the development, manufacture or sale of our product candidates and the associated timing thereof, including the design and results of pre-clinical and clinical studies;
- the safety profile and related adverse events of our product candidates;
- the efficacy and perceived therapeutic benefits of our product candidates and the potential indications and market opportunities therefor;
- U.S. and foreign regulatory requirements for our product candidates, including any post-approval development and regulatory requirements, and the ability of our product candidates to meet such requirements;
- our ability to attract and retain key employees needed to execute our business plans and strategies and our expectations regarding our ability to manage the impact of any loss of key employees;
- our ability to obtain and maintain intellectual property protection for our product candidates and the strength thereof;
- our future financial performance, revenues, expense levels, payments, cash flows, profitability, tax obligations, capital raising and liquidity sources, real estate needs and concentration of voting control, as well as the timing and drivers thereof, and internal control over financial reporting;
- our ability to compete with other companies that are or may be developing or selling products that are competitive with our product candidates;
- the status of government regulation in the life sciences industry, particularly with respect to healthcare reform;
- the potential benefits of strategic collaboration agreements;
- potential indemnification liabilities 2seventy bio may owe to bluebird bio after the separation;

- the tax treatment of the distribution and the limitations imposed on 2seventy bio under the tax matters agreement that 2seventy bio entered into with bluebird bio in connection with the separation and distribution; and
- trends and challenges in our potential markets.

The forward-looking statements in this prospectus represent our views as of the date of this prospectus. We anticipate that subsequent events and developments will cause our views to change. However, while we may elect to update these forward-looking statements at some point in the future, we have no current intention of doing so except to the extent required by applicable law. You should therefore not rely on these forward-looking statements as representing our views as of any date subsequent to the date of this prospectus.

We may from time-to-time provide estimates, projections and other information concerning our industry, our business and the markets for our programs and product candidates. Information that is based on estimates, forecasts, projections, market research or similar methodologies is inherently subject to uncertainties and actual events or circumstances may differ materially from events and circumstances that are assumed in this information. Unless otherwise expressly stated, we obtained this industry, business, market, and other data from our own internal estimates and research as well as from reports, research surveys, studies, and similar data prepared by market research firms and other third parties, industry, medical and general publications, government data and similar sources. While we are not aware of any misstatements regarding any third-party information presented in this prospectus, their estimates, in particular, as they relate to projections, involve numerous assumptions, are subject to risks and uncertainties and are subject to change based on various factors. You should read this prospectus, any applicable prospectus supplement and any related free writing prospectus and the documents that we reference therein and have filed with the SEC as exhibits thereto completely and with the understanding that our actual future results may be materially different from any future results expressed or implied by these forward-looking statements. These estimates involve numerous assumptions, are subject to risks and uncertainties and are subject to change based on various factors, including those discussed under Part I, Item 1A “Risk Factors” and elsewhere in our most recent Annual Report on Form 10-K, our subsequent Quarterly Reports on Form 10-Q and our Current Reports on Form 8-K, and the section of any accompanying prospectus supplement entitled “Risk Factors.”

OUR COMPANY

Overview

We are a cell and gene therapy company focused on the research, development, and commercialization of transformative treatments for cancer. We are led by an accomplished team with significant expertise and experience in this field, from discovery through clinical development to regulatory approval of *ABECMA* (idecabtagene vicleucel, or ide-cel), the first chimeric antigen receptor, or CAR T, cell therapy approved by the U.S. Food and Drug Administration, or FDA, for multiple myeloma. Our approach combines our expertise in T cell engineering technology and lentiviral vector gene delivery approaches, experience in research, development, and manufacturing of cell therapies and a suite of technologies that can be selectively deployed to develop highly innovative, targeted cellular therapies for patients with cancer. We are advancing multiple clinical programs, including DARIC33, for the treatment of pediatric patients with relapsed and refractory acute myeloid leukemia and bbT369, for the treatment of patients with B-cell non-Hodgkins lymphoma as well as multiple preclinical programs, including bbT4015, an engineered CAR T cell therapy targeting MUC16. Additionally, together with our partner Bristol-Myers Squibb, or BMS, we are delivering *ABECMA* to multiple myeloma patients in the United States following approval by the FDA of *ABECMA* in March 2021 for the treatment of adults with multiple myeloma who have received at least four prior lines of therapy, including an immunomodulatory agent, a proteasome inhibitor and an anti-CD38 (cyclic ADP ribose hydrolase) monoclonal antibody.

Corporate History

2seventy bio, Inc. was incorporated in the State of Delaware on April 26, 2021 for the purpose of holding bluebird bio, Inc.’s oncology portfolio and programs in connection with the separation of bluebird bio’s oncology portfolio and programs from its severe genetic disease portfolio and programs. The contribution of this business to us occurred over a period of time prior to the completion of the separation, and we had no operations prior to such contribution. In that regard, on November 3, 2021, the Company entered into a separation agreement with bluebird bio, and on November 4, 2021, each bluebird bio stockholder received a pro rata share of 2seventy bio's common stock for every share of bluebird bio common stock held of record at the close of business on the record date for such distribution. As a result of such distribution, 2seventy bio became an independent, publicly traded company.

The address of our principal executive offices is 60 Binney Street, Cambridge, Massachusetts 02142. We also maintain a website at www.2seventybio.com. The information contained in or accessible from our website is not incorporated into this prospectus, and you should not consider it part of this prospectus. We have included our website address in this prospectus solely as an inactive textual reference.

We use various trademarks and trade names in our business, including without limitation our corporate name and logo. All other trademarks or trade names referred to in this prospectus are the property of their respective owners. Solely for convenience, the trademarks and trade names in this prospectus may be referred to without the ® and ™ symbols, but such references should not be construed as any indicator that their respective owners will not assert, to the fullest extent under applicable law, their rights thereto.

Implications of Being an Emerging Growth Company

We qualify as an “emerging growth company” as defined in the Jumpstart Our Business Startups Act of 2012, as amended (the “JOBS Act”). As an emerging growth company, we may take advantage of specified reduced disclosure and other requirements that are otherwise applicable generally to public companies. These provisions include:

- being permitted to only disclose two years of audited financial statements in addition to any required unaudited interim financial statements with correspondingly reduced “Management’s Discussion and Analysis of Financial Condition and Results of Operations” disclosure;
- reduced disclosure about our executive compensation arrangements;

- not being required to hold advisory votes on executive compensation or to obtain stockholder approval of any golden parachute arrangements not previously approved; and
- an exemption from the auditor attestation requirement in the assessment of our internal control over financial reporting.

We would cease to be an emerging growth company on the date that is the earliest of (i) the last day of the fiscal year in which we have total annual gross revenue of $1.235 billion or more; (ii) December 31, 2025; (iii) the date on which we have issued more than $1.0 billion in nonconvertible debt during the previous three years; or (iv) the last day of the fiscal year in which we are deemed to be a large accelerated filer under the rules of the SEC, which means the market value of our common stock that is held by non-affiliates exceeds $700 million as of the prior June 30th. We may choose to take advantage of some but not all of these exemptions. We have taken advantage of reduced reporting requirements in this prospectus. Accordingly, the information contained herein may be different from the information you receive from other public companies in which you hold stock. We are in the process of evaluating the benefits of relying on other exemptions and reduced reporting requirements under the JOBS Act. Subject to certain conditions, as an emerging growth company, we may rely on certain of these exemptions, including without limitation, providing an auditor's attestation report on our system of internal controls over financial reporting pursuant to Section 404(b) of the Sarbanes-Oxley Act of 2002.

USE OF PROCEEDS

We intend to use the net proceeds from the sale of any securities offered under this prospectus for general corporate purposes unless otherwise indicated in the applicable prospectus supplement. General corporate purposes may include research and development and clinical development costs to support the advancement of our product candidates and the expansion of our research and development programs; commercial activities in support of our approved product candidate; working capital; capital expenditures; and other general corporate purposes. We may temporarily invest the net proceeds in a variety of capital preservation instruments, including short-term, investment-grade, interest-bearing instruments and U.S. government securities, or may hold such proceeds as cash, until they are used for their stated purpose. We have not determined the amount of net proceeds to be used specifically for such purposes. As a result, management will retain broad discretion over the allocation of net proceeds.

SECURITIES THAT MAY BE OFFERED

This prospectus contains summary descriptions of the securities we may offer from time to time. These summary descriptions are not meant to be complete descriptions of each security. The particular terms of any security will be described in the applicable prospectus supplement. This prospectus provides you with a general description of the securities we may offer. Each time we sell securities described herein, we will provide prospective investors with a supplement to this prospectus that will contain specific information about the terms of that offering, including the specific amounts, prices and terms of the securities offered.

We may sell the securities to or through underwriters, dealers or agents, directly to purchasers or through a combination of any of these methods of sale or as otherwise set forth below under “Plan of Distribution.” We, as well as any agents acting on our behalf, reserve the sole right to accept and to reject in whole or in part any proposed purchase of securities. Any prospectus supplement will set forth the names of any underwriters, dealers, agents or other entities involved in the sale of securities described in that prospectus supplement and any applicable fee, commission or discount arrangements with them.

DESCRIPTION OF CAPITAL STOCK

The following description of our capital stock is intended as a summary only and therefore is not a complete description of our capital stock. This description is based upon, and is qualified by reference to, our certificate of incorporation, our bylaws, and applicable provisions of Delaware corporate law. You should read our certificate of incorporation and our bylaws, in each case, as amended and supplemented, which are filed as exhibits to the registration statement of which this prospectus forms a part, for the provisions that are important to you.

General

Our authorized capital stock consists of 200,000,000 shares of common stock, par value $0.0001 per share, and 10,000,000 shares of preferred stock, par value $0.0001 per share, all of which shares of preferred stock are undesignated.

As of November 1, 2022, 37,916,693 shares of our common stock were outstanding and held by 12 stockholders of record.

Common Stock

The holders of our common stock are entitled to one vote for each share held on all matters submitted to a vote of the stockholders. The holders of our common stock do not have any cumulative voting rights. Holders of our common stock are entitled to receive ratably any dividends declared by our board of directors out of funds legally available for that purpose, subject to any preferential dividend rights of any outstanding preferred stock. Our common stock has no preemptive rights, conversion rights or other subscription rights or redemption or sinking fund provisions.

In the event of our liquidation, dissolution or winding up, holders of our common stock will be entitled to share ratably in all assets remaining after payment of all debts and other liabilities and any liquidation preference of any outstanding preferred stock.

Preferred Stock

Our board of directors has the authority, without further action by our stockholders, to issue up to 10,000,000 shares of preferred stock in one or more series and to fix the rights, preferences, privileges and restrictions thereof. These rights, preferences and privileges could include dividend rights, conversion rights, voting rights, terms of redemption, liquidation preferences, sinking fund terms and the number of shares constituting, or the designation of, such series, any or all of which may be greater than the rights of common stock. The issuance of our preferred stock could adversely affect the voting power of holders of common stock and the likelihood that such holders will receive dividend payments and payments upon our liquidation. In addition, the issuance of preferred stock could have the effect of delaying, deferring or preventing a change in control of our Company or other corporate action. Immediately after consummation of this offering, no shares of preferred stock will be outstanding, and we have no present plan to issue any shares of preferred stock.

Registration Rights

In connection with our separation from bluebird bio, Inc., or bluebird bio, we entered into an assumption agreement pursuant to which we assumed all of bluebird bio's obligations (1) under the registration rights agreement that bluebird bio entered into on September 10, 2021 with certain institutional investors, solely in connection with the shares of our common stock that the institutional investors received in the distribution with respect to the shares of bluebird bio common stock they held as of the record date for the distribution and any shares of our common stock that the institutional investors receive upon exercise of the pre-funded warrants that we issued to such institutional investors in connection with the separation and pursuant to the terms of the securities purchase agreement, dated September 10, 2021, by and among bluebird bio and such institutional investors and (2) under Article IV of the securities purchase agreement in connection with the shares of our common stock that the institutional investors received in the distribution with respect to the shares of bluebird bio common stock they held as of the record date for the distribution and any shares of our common stock that the institutional investors receive

upon exercise of the pre-funded warrants we issued to them. Pursuant to the registration rights agreement and the assumed provisions of the securities purchase agreement, following demand by any investor at any time such investor could reasonably be deemed to be an affiliate (as defined and used in Rule 144 as promulgated under the Securities Act) of the Company, we agreed to (i) file with the SEC a Registration Statement on Form S-3 covering the resale of the shares of our common stock issued to it in the distribution in respect of the purchased shares of bluebird bio common stock or issuable upon exercise of the pre-funded warrants by the investors as promptly as reasonably practicable following such demand, and in any event within 60 days after such demand, or (ii) to effect one underwritten offering per calendar year, but no more than three underwritten offerings in total, and no more than two underwritten offerings or block trades in any twelve month period.

Certain holders of our common stock are entitled to rights with respect to the registration of these securities under the Securities Act. These rights are provided under the terms of a registration rights agreement entered into in connection with the March 2022 private placement (the "PIPE Registration Rights") Pursuant to the PIPE Registration Rights Agreement, we prepared and filed a registration statement on Form S-1 with the SEC within 45 calendar days following the closing of the March 2022 private placement of an aggregate of 13,934,427 shares of our common stock to certain holders at a purchase price of $12.20 per share, which Form S-1 was declared effective by the SEC on May 6, 2022. Subsequently, pursuant to the PIPE Registration Rights Agreement, we converted the Form S-1 to Form S-3, when we became eligible to use Form S-3 by filing a Post-Effective Amendment to the Form S-1. All fees, costs and expenses of underwritten registrations under the PIPE Registration Rights Agreement will be borne by us.

Anti-Takeover Effects of our Certificate of Incorporation and Bylaws and Delaware Law

Our certificate of incorporation and bylaws include a number of provisions that may have the effect of delaying, deferring or preventing another party from acquiring control of us and encouraging persons considering unsolicited tender offers or other unilateral takeover proposals to negotiate with our board of directors rather than pursue non-negotiated takeover attempts. These provisions include certain items described below.

Board Composition and Filling Vacancies

Our certificate of incorporation provides for the division of our board of directors into three classes serving staggered three-year terms, with one class being elected each year. Our certificate of incorporation also provides that directors may be removed only for cause and then only by the affirmative vote of the holders of two-thirds or more of the shares then entitled to vote at an election of directors. Furthermore, any vacancy on our board of directors, however occurring, including a vacancy resulting from an increase in the size of our board, may only be filled by the affirmative vote of a majority of our directors then in office even if less than a quorum. The classification of directors, together with the limitations on removal of directors and treatment of vacancies, has the effect of making it more difficult for stockholders to change the composition of our board of directors.

No Written Consent of Stockholders

Our certificate of incorporation provides that all stockholder actions are required to be taken by a vote of the stockholders at an annual or special meeting, and that stockholders may not take any action by written consent in lieu of a meeting. This limit may lengthen the amount of time required to take stockholder actions and would prevent the amendment of our bylaws or removal of directors by our stockholders without holding a meeting of stockholders.

Meetings of Stockholders

Our certificate of incorporation and bylaws provide that only a majority of the members of our board of directors then in office may call special meetings of stockholders and only those matters set forth in the notice of the special meeting may be considered or acted upon at a special meeting of stockholders. Our bylaws limit the business that may be conducted at an annual meeting of stockholders to those matters properly brought before the meeting.

Advance Notice Requirements

Our bylaws establish advance notice procedures with regard to stockholder proposals relating to the nomination of candidates for election as directors or new business to be brought before meetings of our stockholders. These procedures provide that notice of stockholder proposals must be timely given in writing to our corporate secretary prior to the meeting at which the action is to be taken. Generally, to be timely, notice must be received at our principal executive offices not less than 90 days nor more than 120 days prior to the first anniversary date of the annual meeting for the preceding year. Our bylaws specify the requirements as to form and content of all stockholders' notices. These requirements may preclude stockholders from bringing matters before the stockholders at an annual or special meeting.

Anti-Takeover Effects of Provisions of Our Charter Documents

Any amendment of our certificate of incorporation must first be approved by a majority of our board of directors, and if required by law or our certificate of incorporation, must thereafter be approved by a majority of the outstanding shares entitled to vote on the amendment and a majority of the outstanding shares of each class entitled to vote thereon as a class, except that the amendment of the provisions relating to stockholder action, board composition, and limitation of liability must be approved by not less than two-thirds of the outstanding shares entitled to vote on the amendment, and not less than two-thirds of the outstanding shares of each class entitled to vote thereon as a class. Our bylaws may be amended or repealed by the affirmative vote of a majority of the directors then in office, subject to any limitations set forth in the bylaws; and may also be amended or repealed by the affirmative vote of at least seventy-five percent of the outstanding shares entitled to vote on the amendment or repeal, voting together as a single class, or, if our board of directors recommends that the stockholders approve or repeal the amendment, by the affirmative vote of the majority of the outstanding shares entitled to vote on the amendment or repeal, in each case voting together as a single class.

Undesignated Preferred Stock

Our certificate of incorporation provides for 10,000,000 authorized shares of preferred stock. The existence of authorized but unissued shares of preferred stock may enable our board of directors to discourage an attempt to obtain control of us by means of a merger, tender offer, proxy contest or otherwise. For example, if in the due exercise of its fiduciary obligations, our board of directors were to determine that a takeover proposal is not in the best interests of our stockholders, our board of directors could cause shares of preferred stock to be issued without stockholder approval in one or more private offerings or other transactions that might dilute the voting or other rights of the proposed acquirer or insurgent stockholder or stockholder group. In this regard, our certificate of incorporation grants our board of directors broad power to establish the rights and preferences of authorized and unissued shares of preferred stock. The issuance of shares of preferred stock could decrease the amount of earnings and assets available for distribution to holders of shares of common stock. The issuance may also adversely affect the rights and powers, including voting rights, of these holders and may have the effect of delaying, deterring or preventing a change in control of us.

Choice of Forum

Our bylaws provide that, unless we consent in writing to the selection of an alternative forum, the Court of Chancery of the State of Delaware, or the Chancery Court, will be the sole and exclusive forum for state law claims for (i) any derivative action or proceeding brought on our behalf, (ii) any action asserting a claim of, or a claim based on, a breach of a fiduciary duty owed by any of our directors, officers or other employees to us or our stockholders, (iii) any action asserting a claim pursuant to any provision of the Delaware General Corporation Law, our certificate of incorporation or our bylaws, (iv) any action to interpret, apply, enforce or determine the validity of our certificate of incorporation or bylaws, or (v) any action asserting a claim governed by the internal affairs doctrine, or the Delaware Forum Provision. The Delaware Forum Provision does not apply to any causes of action arising under the Securities Act of 1933, as amended, or the Securities Act, or the Exchange Act. Our bylaws further provide that, unless we consent in writing to the selection of an alternative forum, the federal district courts of the United States of America will be the sole and exclusive forum for resolving any complaint asserting a cause of action arising under the Securities Act, or the Federal Forum Provision. Our bylaws provide that any person or entity

purchasing or otherwise acquiring any interest in shares of our capital stock is deemed to have notice of and consented to the foregoing Delaware Forum Provision and the Federal Forum Provision; provided, however, that stockholders cannot and will not be deemed to have waived our compliance with the federal securities laws and the rules and regulations thereunder.

Section 203 of the Delaware General Corporation Law

We are subject to the provisions of Section 203 of the Delaware General Corporation Law. In general, Section 203 prohibits a publicly held Delaware corporation from engaging in a "business combination" with an "interested stockholder" for a three-year period following the time that this stockholder becomes an interested stockholder, unless the business combination is approved in a prescribed manner. Under Section 203, a business combination between a corporation and an interested stockholder is prohibited unless it satisfies one of the following conditions:

- before the stockholder became interested, our board of directors 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, shares owned by persons who are directors and also officers, and employee stock plans, in some instances, but not the outstanding voting stock owned by the interested stockholder; or;
- at or after the time the stockholder became interested, the business combination was approved by our board of directors and authorized at an annual or special meeting of the stockholders by the affirmative vote of at least two-thirds 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; or
- any sale, transfer, lease, pledge or other disposition involving the interested stockholder of 10% or more of the assets of the corporation;
- 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
- 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
- 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.

Stock Exchange Listing

Our common stock is listed on The Nasdaq Global Select Market under the trading symbol "TSVT."

Transfer Agent and Registrar

The transfer agent and registrar for our common stock is American Stock Transfer & Trust Company, LLC. The transfer agent and registrar's address is 6201 15th Avenue, Brooklyn, NY 11219.

DESCRIPTION OF DEBT SECURITIES

We may issue debt securities from time to time, in one or more series, as either senior or subordinated debt or as senior or subordinated convertible debt. While the terms we have summarized below will apply generally to any debt securities that we may offer under this prospectus, we will describe the particular terms of any debt securities that we may offer in more detail in the applicable prospectus supplement. The terms of any debt securities offered under a prospectus supplement may differ from the terms described below. Unless the context requires otherwise, whenever we refer to the indenture, we also are referring to any supplemental indentures that specify the terms of a particular series of debt securities.

We will issue the debt securities under the indenture that we will enter into with the trustee named in the indenture. The indenture will be qualified under the Trust Indenture Act of 1939, as amended (the "Trust Indenture Act"). We have filed the form of indenture as an exhibit to the registration statement of which this prospectus is a part, and supplemental indentures and forms of debt securities containing the terms of the debt securities being offered will be filed as exhibits to the registration statement of which this prospectus is a part, or will be incorporated by reference from, reports that we file with the SEC.

The following summary of material provisions of the debt securities and the indenture is subject to, and qualified in its entirety by reference to, all of the provisions of the indenture applicable to a particular series of debt securities. We urge you to read the applicable prospectus supplements and any related free writing prospectuses related to the debt securities that we may offer under this prospectus, as well as the complete indenture that contains the terms of the debt securities.

General

The indenture does not limit the amount of debt securities that we may issue. It provides that we may issue debt securities up to the principal amount that we may authorize and may be in any currency or currency unit that we may designate. Except for the limitations on consolidation, merger and sale of all or substantially all of our assets contained in the indenture, the terms of the indenture do not contain any covenants or other provisions designed to give holders of any debt securities protection against changes in our operations, financial condition or transactions involving us.

We may issue the debt securities issued under the indenture as "discount securities," which means they may be sold at a discount below their stated principal amount. These debt securities, as well as other debt securities that are not issued at a discount, may be issued with "original issue discount" ("OID") for U.S. federal income tax purposes because of interest payment and other characteristics or terms of the debt securities. Material U.S. federal income tax considerations applicable to debt securities issued with OID will be described in more detail in any applicable prospectus supplement.

We will describe in the applicable prospectus supplement the terms of the series of debt securities being offered, including:

- the title of the series of debt securities;
- any limit upon the aggregate principal amount that may be issued;
- the maturity date or dates;
- the form of the debt securities of the series;
- the applicability of any guarantees;
- whether or not the debt securities will be secured or unsecured, and the terms of any secured debt;
- whether the debt securities rank as senior debt, senior subordinated debt, subordinated debt or any combination thereof, and the terms of any subordination;

- if the price (expressed as a percentage of the aggregate principal amount thereof) at which such debt securities will be issued is a price other than the principal amount thereof, the portion of the principal amount thereof payable upon declaration of acceleration of the maturity thereof, or if applicable, the portion of the principal amount of such debt securities that is convertible into another security or the method by which any such portion shall be determined;
- the interest rate or rates, which may be fixed or variable, or the method for determining the rate and the date interest will begin to accrue, the dates interest will be payable and the regular record dates for interest payment dates or the method for determining such dates;
- our right, if any, to defer payment of interest and the maximum length of any such deferral period;
- if applicable, the date or dates after which, or the period or periods during which, and the price or prices at which, we may, at our option, redeem the series of debt securities pursuant to any optional or provisional redemption provisions and the terms of those redemption provisions;
- the date or dates, if any, on which, and the price or prices at which we are obligated, pursuant to any mandatory sinking fund or analogous fund provisions or otherwise, to redeem, or at the holder's option to purchase, the series of debt securities and the currency or currency unit in which the debt securities are payable;
- the denominations in which we will issue the series of debt securities, if other than denominations of $1,000 and any integral multiple thereof;
- any and all terms, if applicable, relating to any auction or remarketing of the debt securities of that series and any security for our obligations with respect to such debt securities and any other terms which may be advisable in connection with the marketing of debt securities of that series;
- whether the debt securities of the series shall be issued in whole or in part in the form of a global security or securities; the terms and conditions, if any, upon which such global security or securities may be exchanged in whole or in part for other individual securities; and the depositary for such global security or securities;
- if applicable, the provisions relating to conversion or exchange of any debt securities of the series and the terms and conditions upon which such debt securities will be so convertible or exchangeable, including the conversion or exchange price, as applicable, or how it will be calculated and may be adjusted, any mandatory or optional (at our option or the holders' option) conversion or exchange features, the applicable conversion or exchange period and the manner of settlement for any conversion or exchange;
- if other than the full principal amount thereof, the portion of the principal amount of debt securities of the series which shall be payable upon declaration of acceleration of the maturity thereof;
- additions to or changes in the covenants applicable to the particular debt securities being issued, including, among others, the consolidation, merger or sale covenant;
- additions to or changes in the events of default with respect to the securities and any change in the right of the trustee or the holders to declare the principal, premium, if any, and interest, if any, with respect to such securities to be due and payable;
- additions to or changes in or deletions of the provisions relating to covenant defeasance and legal defeasance;
- additions to or changes in the provisions relating to satisfaction and discharge of the indenture;
- additions to or changes in the provisions relating to the modification of the indenture both with and without the consent of holders of debt securities issued under the indenture;

- the currency of payment of debt securities if other than U.S. dollars and the manner of determining the equivalent amount in U.S. dollars;
- whether interest will be payable in cash or additional debt securities at our or the holders' option and the terms and conditions upon which the election may be made;
- the terms and conditions, if any, upon which we will pay amounts in addition to the stated interest, premium, if any and principal amounts of the debt securities of the series to any holder that is not a "United States person" for federal tax purposes;
- any restrictions on transfer, sale or assignment of the debt securities of the series; and
- any other specific terms, preferences, rights or limitations of, or restrictions on, the debt securities, any other additions or changes in the provisions of the indenture, and any terms that may be required by us or advisable under applicable laws or regulations.

Conversion or Exchange Rights

We will set forth in the applicable prospectus supplement the terms on which a series of debt securities may be convertible into or exchangeable for our common stock or our other securities. We will include provisions as to settlement upon conversion or exchange and whether conversion or exchange is mandatory, at the option of the holder or at our option. We may include provisions pursuant to which the number of shares of our common stock or our other securities that the holders of the series of debt securities receive would be subject to adjustment.

Consolidation, Merger or Sale

Unless we provide otherwise in the prospectus supplement applicable to a particular series of debt securities, the indenture will not contain any covenant that restricts our ability to merge or consolidate, or sell, convey, transfer or otherwise dispose of our assets as an entirety or substantially as an entirety. However, any successor to or acquirer of such assets (other than any subsidiary of ours) must assume all of our obligations under the indenture or the debt securities, as appropriate.

Events of Default under the Indenture

Unless we provide otherwise in the prospectus supplement applicable to a particular series of debt securities, the following are events of default under the indenture with respect to any series of debt securities that we may issue:

- if we fail to pay any installment of interest on any series of debt securities, as and when the same shall become due and payable, and such default continues for a period of 90 days; provided, however, that a valid extension of an interest payment period by us in accordance with the terms of any indenture supplemental thereto shall not constitute a default in the payment of interest for this purpose;
- if we fail to pay the principal of, or premium, if any, on any series of debt securities as and when the same shall become due and payable whether at maturity, upon redemption, by declaration or otherwise, or in any payment required by any sinking or analogous fund established with respect to such series; provided, however, that a valid extension of the maturity of such debt securities in accordance with the terms of any indenture supplemental thereto shall not constitute a default in the payment of principal or premium, if any;
- if we fail to observe or perform any other covenant or agreement contained in the debt securities or the indenture, other than a covenant specifically relating to another series of debt securities, and our failure continues for 90 days after we receive written notice of such failure, requiring the same to be remedied and stating that such is a notice of default thereunder, from the trustee or holders of at least 25% in aggregate principal amount of the outstanding debt securities of the applicable series; and
- if specified events of bankruptcy, insolvency or reorganization occur.

If an event of default with respect to debt securities of any series occurs and is continuing, other than an event of default specified in the last bullet point above, the trustee or the holders of at least 25% in aggregate principal amount of the outstanding debt securities of that series, by notice to us in writing, and to the trustee if notice is given by such holders, may declare the unpaid principal of, premium, if any, and accrued interest, if any, due and payable immediately. If an event of default specified in the last bullet point above occurs with respect to us, the principal amount of and accrued interest, if any, of each issue of debt securities then outstanding shall be due and payable without any notice or other action on the part of the trustee or any holder.

The holders of a majority in principal amount of the outstanding debt securities of an affected series may waive any default or event of default with respect to the series and its consequences, except defaults or events of default regarding payment of principal, premium, if any, or interest, unless we have cured the default or event of default in accordance with the indenture. Any waiver shall cure the default or event of default.

Subject to the terms of the indenture, if an event of default under an indenture shall occur and be continuing, the trustee will be under no obligation to exercise any of its rights or powers under such indenture at the request or direction of any of the holders of the applicable series of debt securities, unless such holders have offered the trustee reasonable indemnity. The holders of a majority in principal amount of the outstanding debt securities of any series will have the right to direct the time, method and place of conducting any proceeding for any remedy available to the trustee, or exercising any trust or power conferred on the trustee, with respect to the debt securities of that series, provided that:

- the direction so given by the holder is not in conflict with any law or the applicable indenture; and
- subject to its duties under the Trust Indenture Act, the trustee need not take any action that might involve it in personal liability or might be unduly prejudicial to the holders not involved in the proceeding.

A holder of the debt securities of any series will have the right to institute a proceeding under the indenture or to appoint a receiver or trustee, or to seek other remedies only if:

- the holder has given written notice to the trustee of a continuing event of default with respect to that series;
- the holders of at least 25% in aggregate principal amount of the outstanding debt securities of that series have made written request,
- such holders have offered to the trustee indemnity satisfactory to it against the costs, expenses and liabilities to be incurred by the trustee in compliance with the request; and
- the trustee does not institute the proceeding, and does not receive from the holders of a majority in aggregate principal amount of the outstanding debt securities of that series other conflicting directions within 90 days after the notice, request and offer.

These limitations do not apply to a suit instituted by a holder of debt securities if we default in the payment of the principal, premium, if any, or interest on, the debt securities.

We will periodically file statements with the trustee regarding our compliance with specified covenants in the indenture.

Modification of Indenture; Waiver

We and the trustee may change an indenture without the consent of any holders with respect to specific matters:

- to cure any ambiguity, defect or inconsistency in the indenture or in the debt securities of any series;
- to comply with the provisions described above under “Description of Debt Securities—Consolidation, Merger or Sale”;
- to provide for uncertificated debt securities in addition to or in place of certificated debt securities;

- to comply with the provisions described above under “Description of Debt Securities—Consolidation, Merger or Sale”;
- to provide for uncertificated debt securities in addition to or in place of certificated debt securities;
- to add to our covenants, restrictions, conditions or provisions such new covenants, restrictions, conditions or provisions for the benefit of the holders of all or any series of debt securities, to make the occurrence, or the occurrence and the continuance, of a default in any such additional covenants, restrictions, conditions or provisions an event of default or to surrender any right or power conferred upon us in the indenture;
- to add to, delete from or revise the conditions, limitations, and restrictions on the authorized amount, terms, or purposes of issue, authentication and delivery of debt securities, as set forth in the indenture;
- to make any change that does not adversely affect the interests of any holder of debt securities of any series in any material respect;
- to provide for the issuance of and establish the form and terms and conditions of the debt securities of any series as provided above under “Description of Debt Securities—General” to establish the form of any certifications required to be furnished pursuant to the terms of the indenture or any series of debt securities, or to add to the rights of the holders of any series of debt securities;
- to evidence and provide for the acceptance of appointment under any indenture by a successor trustee; or
- to comply with any requirements of the SEC in connection with the qualification of any indenture under the Trust Indenture Act.

In addition, under the indenture, the rights of holders of a series of debt securities may be changed by us and the trustee with the written consent of the holders of at least a majority in aggregate principal amount of the outstanding debt securities of each series that is affected. However, unless we provide otherwise in the prospectus supplement applicable to a particular series of debt securities, we and the trustee may make the following changes only with the consent of each holder of any outstanding debt securities affected:

- extending the fixed maturity of any debt securities of any series;
- reducing the principal amount, reducing the rate of or extending the time of payment of interest, or reducing any premium payable upon the redemption of any series of any debt securities; or
- reducing the percentage of debt securities, the holders of which are required to consent to any amendment, supplement, modification or waiver.

Discharge

Each indenture provides that we can elect to be discharged from our obligations with respect to one or more series of debt securities, except for specified obligations, including obligations to:

- provide for payment;
- register the transfer or exchange of debt securities of the series;
- replace stolen, lost or mutilated debt securities of the series;
- pay principal of and premium and interest on any debt securities of the series;
- maintain paying agencies;
- hold monies for payment in trust;
- recover excess money held by the trustee;

- compensate and indemnify the trustee; and
- appoint any successor trustee.

In order to exercise our rights to be discharged, we must deposit with the trustee money or government obligations sufficient to pay all the principal of, any premium, if any, and interest on, the debt securities of the series on the dates payments are due.

Form, Exchange and Transfer

We will issue the debt securities of each series only in fully registered form without coupons and, unless we provide otherwise in the applicable prospectus supplement, in denominations of $1,000 and any integral multiple thereof. The indenture provides that we may issue debt securities of a series in temporary or permanent global form and as book-entry securities that will be deposited with, or on behalf of, The Depository Trust Company ("DTC") or another depositary named by us and identified in the applicable prospectus supplement with respect to that series. To the extent the debt securities of a series are issued in global form and as book-entry, a description of terms relating to any book-entry securities will be set forth in the applicable prospectus supplement.

At the option of the holder, subject to the terms of the indenture and the limitations applicable to global securities described in the applicable prospectus supplement, the holder of the debt securities of any series can exchange the debt securities for other debt securities of the same series, in any authorized denomination and of like tenor and aggregate principal amount.

Subject to the terms of the indenture and the limitations applicable to global securities set forth in the applicable prospectus supplement, holders of the debt securities may present the debt securities for exchange or for registration of transfer, duly endorsed or with the form of transfer endorsed thereon duly executed if so required by us or the security registrar, at the office of the security registrar or at the office of any transfer agent designated by us for this purpose. Unless otherwise provided in the debt securities that the holder presents for transfer or exchange, we will impose no service charge for any registration of transfer or exchange, but we may require payment of any taxes or other governmental charges.

We will name in the applicable prospectus supplement the security registrar, and any transfer agent in addition to the security registrar, that we initially designate for any debt securities. We may at any time designate additional transfer agents or rescind the designation of any transfer agent or approve a change in the office through which any transfer agent acts, except that we will be required to maintain a transfer agent in each place of payment for the debt securities of each series.

If we elect to redeem the debt securities of any series, we will not be required to:

- issue, register the transfer of, or exchange any debt securities of that series during a period beginning at the opening of business 15 days before the day of mailing of a notice of redemption of any debt securities that may be selected for redemption and ending at the close of business on the day of the mailing; or
- register the transfer of or exchange any debt securities so selected for redemption, in whole or in part, except the unredeemed portion of any debt securities we are redeeming in part.

Information Concerning the Trustee

The trustee, other than during the occurrence and continuance of an event of default under an indenture, undertakes to perform only those duties as are specifically set forth in the applicable indenture. Upon an event of default under an indenture, the trustee must use the same degree of care as a prudent person would exercise or use in the conduct of his or her own affairs. Subject to this provision, the trustee is under no obligation to exercise any of the powers given it by the indenture at the request of any holder of debt securities unless it is offered reasonable security and indemnity against the costs, expenses and liabilities that it might incur.

Payment and Paying Agents

Unless we otherwise indicate in the applicable prospectus supplement, we will make payment of the interest on any debt securities on any interest payment date to the person in whose name the debt securities, or one or more predecessor securities, are registered at the close of business on the regular record date for the interest.

We will pay principal of and any premium and interest on the debt securities of a particular series at the office of the paying agents designated by us, except that unless we otherwise indicate in the applicable prospectus supplement, we will make interest payments by check that we will mail to the holder or by wire transfer to certain holders. Unless we otherwise indicate in the applicable prospectus supplement, we will designate the corporate trust office of the trustee as our sole paying agent for payments with respect to debt securities of each series. We will name in the applicable prospectus supplement any other paying agents that we initially designate for the debt securities of a particular series. We will maintain a paying agent in each place of payment for the debt securities of a particular series.

All money we pay to a paying agent or the trustee for the payment of the principal of or any premium or interest on any debt securities that remains unclaimed at the end of two years after such principal, premium or interest has become due and payable will be repaid to us, and the holder of the debt security thereafter may look only to us for payment thereof.

Governing Law

The indenture and the debt securities will be governed by and construed in accordance with the laws of the state of New York, except to the extent that the Trust Indenture Act is applicable.

DESCRIPTION OF WARRANTS

The following description, together with the additional information we may include in any applicable prospectus supplements, summarizes the material terms and provisions of the warrants that we may offer under this prospectus and the related warrant agreements and warrant certificates. While the terms summarized below will apply generally to any warrants that we may offer, we will describe the particular terms of any series of warrants in more detail in the applicable prospectus supplement. If we indicate in the prospectus supplement, the terms of any warrants offered under that prospectus supplement may differ from the terms described below. Specific warrant agreements will contain additional important terms and provisions and will be incorporated by reference as an exhibit to the registration statement, which includes this prospectus.

General

We may issue warrants for the purchase of common stock, preferred stock in one or more series. We may issue warrants independently or together with common stock, preferred stock, and the warrants may be attached to or separate from these securities.

We will evidence each series of warrants by warrant certificates that we will issue under a separate warrant agreement. We will enter into the warrant agreement with a warrant agent. We will indicate the name and address of the warrant agent in the applicable prospectus supplement relating to a particular series of warrants.

We will describe in the applicable prospectus supplement the terms of the series of warrants, including:

- the offering price and aggregate number of warrants offered;
- the currency for which the warrants may be purchased;
- if applicable, the designation and terms of the securities with which the warrants are issued and the number of warrants issued with each such security or each principal amount of such security;
- if applicable, the date on and after which the warrants and the related securities will be separately transferable;
- in the case of warrants to purchase common stock or preferred stock, the number of shares of common stock or preferred stock, as the case may be, purchasable upon the exercise of one warrant and the price at which these shares may be purchased upon such exercise;
- in the case of warrants to purchase debt securities, the principal amount of debt securities purchasable upon exercise of one warrant and the price at, and currency in which, this principal amount of debt securities may be purchased upon such exercise;
- the effect of any merger, consolidation, sale or other disposition of our business on the warrant agreement and the warrants;
- the terms of any rights to redeem or call the warrants;
- any provisions for changes to or adjustments in the exercise price or number of securities issuable upon exercise of the warrants;
- the periods during which, and places at which, the warrants are exercisable;
- the manner of exercise;
- the dates on which the right to exercise the warrants will commence and expire;
- the manner in which the warrant agreement and warrants may be modified;
- federal income tax consequences of holding or exercising the warrants;

- the terms of the securities issuable upon exercise of the warrants; and
- any other specific terms, preferences, rights or limitations of or restrictions on the warrants.

DESCRIPTION OF UNITS

We may issue units comprised of shares of common stock, shares of preferred stock and warrants in any combination. We may issue units in such amounts and in as many distinct series as we wish. This section outlines certain provisions of the units that we may issue. If we issue units, they will be issued under one or more unit agreements to be entered into between us and a bank or other financial institution, as unit agent. The information described in this section may not be complete in all respects and is qualified entirely by reference to the unit agreement with respect to the units of any particular series. The specific terms of any series of units offered will be described in the applicable prospectus supplement. If so described in a particular supplement, the specific terms of any series of units may differ from the general description of terms presented below. We urge you to read any prospectus supplement related to any series of units we may offer, as well as the complete unit agreement and unit certificate that contain the terms of the units. If we issue units, forms of unit agreements and unit certificates relating to such units will be incorporated by reference as exhibits to the registration statement, which includes this prospectus.

Each unit that we may issue will be issued so that the holder of the unit is also the holder of each security included in the unit. Thus, the holder of a unit will have the rights and obligations of a holder of each included security. The unit agreement under which a unit is issued may provide that the securities included in the unit may not be held or transferred separately, at any time or at any time before a specified date. The applicable prospectus supplement may describe:

- the designation and terms of the units and of the securities comprising the units, including whether and under what circumstances those securities may be held or transferred separately;
- any provisions of the governing unit agreement;
- the price or prices at which such units will be issued;
- the applicable United States federal income tax considerations relating to the units;
- any provisions for the issuance, payment, settlement, transfer or exchange of the units or of the securities comprising the units; and
- any other terms of the units and of the securities comprising the units.

The provisions described in this section, as well as those described under “Description of Capital Stock,” and “Description of Warrants” will apply to the securities included in each unit, to the extent relevant and as may be updated in any prospectus supplements.

Issuance in Series

We may issue units in such amounts and in as many distinct series as we wish. This section summarizes terms of the units that apply generally to all series. Most of the financial and other specific terms of a particular series of units will be described in the applicable prospectus supplement.

Unit Agreements

We will issue the units under one or more unit agreements to be entered into between us and a bank or other financial institution, as unit agent. We may add, replace or terminate unit agents from time to time. We will identify the unit agreement under which each series of units will be issued and the unit agent under that agreement in the applicable prospectus supplement.

The following provisions will generally apply to all unit agreements unless otherwise stated in the applicable prospectus supplement:

Modification without Consent

We and the applicable unit agent may amend any unit or unit agreement without the consent of any holder:

- to cure any ambiguity; any provisions of the governing unit agreement that differ from those described below;
- to correct or supplement any defective or inconsistent provision; or
- to make any other change that we believe is necessary or desirable and will not adversely affect the interests of the affected holders in any material respect.

We do not need any approval to make changes that affect only units to be issued after the changes take effect. We may also make changes that do not adversely affect a particular unit in any material respect, even if they adversely affect other units in a material respect. In those cases, we do not need to obtain the approval of the holder of the unaffected unit; we need only obtain any required approvals from the holders of the affected units.

Modification with Consent

We may not amend any particular unit or a unit agreement with respect to any particular unit unless we obtain the consent of the holder of that unit, if the amendment would:

- impair any right of the holder to exercise or enforce any right under a security included in the unit if the terms of that security require the consent of the holder to any changes that would impair the exercise or enforcement of that right; or
- reduce the percentage of outstanding units or any series or class the consent of whose holders is required to amend that series or class, or the applicable unit agreement with respect to that series or class, as described below.

Any other change to a particular unit agreement and the units issued under that agreement would require the following approval:

- If the change affects only the units of a particular series issued under that agreement, the change must be approved by the holders of a majority of the outstanding units of that series; or
- If the change affects the units of more than one series issued under that agreement, it must be approved by the holders of a majority of all outstanding units of all series affected by the change, with the units of all the affected series voting together as one class for this purpose.

These provisions regarding changes with majority approval also apply to changes affecting any securities issued under a unit agreement, as the governing document.

In each case, the required approval must be given by written consent.

Unit Agreements Will Not Be Qualified under Trust Indenture Act

No unit agreement will be qualified as an indenture, and no unit agent will be required to qualify as a trustee, under the Trust Indenture Act. Therefore, holders of units issued under unit agreements will not have the protections of the Trust Indenture Act with respect to their units.

Mergers and Similar Transactions Permitted; No Restrictive Covenants or Events of Default

The unit agreements will not restrict our ability to merge or consolidate with, or sell our assets to, another corporation or other entity or to engage in any other transactions. If at any time we merge or consolidate with, or sell our assets substantially as an entirety to, another corporation or other entity, the successor entity will succeed to and assume our obligations under the unit agreements. We will then be relieved of any further obligation under these agreements.

The unit agreements will not include any restrictions on our ability to put liens on our assets, nor will they restrict our ability to sell our assets. The unit agreements also will not provide for any events of default or remedies upon the occurrence of any events of default.

Governing Law

The unit agreements and the units will be governed by New York law.

Form, Exchange and Transfer

We will issue each unit in global—i.e., book-entry—form only. Units in book-entry form will be represented by a global security registered in the name of a depositary, which will be the holder of all the units represented by the global security. Those who own beneficial interests in a unit will do so through participants in the depositary's system, and the rights of these indirect owners will be governed solely by the applicable procedures of the depositary and its participants. We will describe book-entry securities, and other terms regarding the issuance and registration of the units in the applicable prospectus supplement.

Each unit and all securities comprising the unit will be issued in the same form.

If we issue any units in registered, non-global form, the following will apply to them.

The units will be issued in the denominations stated in the applicable prospectus supplement. Holders may exchange their units for units of smaller denominations or combined into fewer units of larger denominations, as long as the total amount is not changed.

- Holders may exchange or transfer their units at the office of the unit agent. Holders may also replace lost, stolen, destroyed or mutilated units at that office. We may appoint another entity to perform these functions or perform them ourselves.
- Holders will not be required to pay a service charge to transfer or exchange their units, but they may be required to pay for any tax or other governmental charge associated with the transfer or exchange. The transfer or exchange, and any replacement, will be made only if our transfer agent is satisfied with the holder's proof of legal ownership. The transfer agent may also require an indemnity before replacing any units.
- If we have the right to redeem, accelerate or settle any units before their maturity, and we exercise our right as to less than all those units or other securities, we may block the exchange or transfer of those units during the period beginning 15 days before the day we mail the notice of exercise and ending on the day of that mailing, in order to freeze the list of holders to prepare the mailing. We may also refuse to register transfers of or exchange any unit selected for early settlement, except that we will continue to permit transfers and exchanges of the unsettled portion of any unit being partially settled. We may also block the transfer or exchange of any unit in this manner if the unit includes securities that are or may be selected for early settlement.

Only the depositary will be entitled to transfer or exchange a unit in global form, since it will be the sole holder of the unit.

Payments and Notices

In making payments and giving notices with respect to our units, we will follow the procedures as described in the applicable prospectus supplement.

PLAN OF DISTRIBUTION

We may sell the securities offered through this prospectus and any accompanying prospectus supplement, if required, in any of the following ways: (i) to or through underwriters or dealers, (ii) directly to purchasers, including our affiliates, (iii) through agents, (iv) in an "at the market offering," within the meaning of Rule 415(a)(4) of the Securities Act or (v) through a combination of any of these methods or any other method permitted by law. The securities may be distributed at a fixed price or prices, which may be changed, market prices prevailing at the time of sale, prices related to the prevailing market prices, or negotiated prices, either:

- on or through the facilities of The Nasdaq Global Market or any other securities exchange or quotation or trading service on which such securities may be listed, quoted or traded at the time of sale; and/or
- to or through a market maker otherwise than on The Nasdaq Global Market or such other securities exchanges or quotation or trading services.

In addition, we may issue the securities as a dividend or distribution or in a subscription rights offering to our existing security holders.

We may directly solicit offers to purchase securities, or agents may be designated to solicit such offers. In the prospectus supplement relating to such offering, we will name any agent that could be viewed as an underwriter under the Securities Act and describe any commissions that we must pay to any such agent. Any such agent will be acting on a best efforts basis for the period of its appointment or, if indicated in the applicable prospectus supplement, on a firm commitment basis. This prospectus may be used in connection with any offering of our securities through any of these methods or other methods described in the applicable prospectus supplement.

Each prospectus supplement will describe the method of distribution of the securities and any applicable restrictions.

The prospectus supplement with respect to the securities of a particular series will describe the terms of the offering of the securities, including the following:

- the name of the agent or any underwriters;
- the public offering or purchase price;
- any discounts and commissions to be allowed or paid to the agent or underwriters;
- all other items constituting underwriting compensation;
- any discounts and commissions to be allowed or paid to dealers; and
- any exchanges on which the securities will be listed.

If any underwriters or agents are used in the sale of the securities in respect of which this prospectus is delivered, we will enter into an underwriting agreement, sales agreement or other agreement with them at the time of sale to them, and we will set forth in the prospectus supplement relating to such offering the names of the underwriters or agents and the terms of the related agreement with them.

In connection with the offering of securities, we may grant to the underwriters an option to purchase additional securities with an additional underwriting commission, as may be set forth in the accompanying prospectus supplement. If we grant any such option, the terms of such option will be set forth in the prospectus supplement for such securities.

If a dealer is used in the sale of the securities in respect of which the prospectus is delivered, we will sell such securities to the dealer, as principal. The dealer, who may be deemed to be an "underwriter" as that term is defined in the Securities Act, may then resell such securities to the public at varying prices to be determined by such dealer at the time of resale.

If we offer securities in a subscription rights offering to our existing security holders, we may enter into a standby underwriting agreement with dealers, acting as standby underwriters. We may pay the standby underwriters a commitment fee for the securities they commit to purchase on a standby basis. If we do not enter into a standby underwriting arrangement, we may retain a dealer-manager to manage a subscription rights offering for us.

Agents, underwriters, dealers and other persons may be entitled under agreements which they may enter into with us to indemnification by us against certain civil liabilities, including liabilities under the Securities Act, and may be customers of, engage in transactions with or perform services for us in the ordinary course of business.

If so indicated in the applicable prospectus supplement, we will authorize underwriters or other persons acting as our agents to solicit offers by certain institutions to purchase securities from us pursuant to delayed delivery contracts providing for payment and delivery on the date stated in the prospectus supplement. Each contract will be for an amount not less than, and the aggregate amount of securities sold pursuant to such contracts shall not be less nor more than, the respective amounts stated in the prospectus supplement. Institutions with whom the contracts, when authorized, may be made include commercial and savings banks, insurance companies, pension funds, investment companies, educational and charitable institutions and other institutions, but shall in all cases be subject to our approval. Delayed delivery contracts will not be subject to any conditions except that:

- the purchase by an institution of the securities covered under that contract shall not at the time of delivery be prohibited under the laws of the jurisdiction to which that institution is subject; and
- if the securities are also being sold to underwriters acting as principals for their own account, the underwriters shall have purchased such securities not sold for delayed delivery. The underwriters and other persons acting as our agents will not have any responsibility in respect of the validity or performance of delayed delivery contracts.

Offered securities may also be offered and sold, if so indicated in the prospectus supplement, in connection with a remarketing upon their purchase, in accordance with a redemption or repayment pursuant to their terms, or otherwise, by one or more remarketing firms, acting as principals for their own accounts or as agents for us. Any remarketing firm will be identified and the terms of its agreement, if any, with us and its compensation will be described in the applicable prospectus supplement. Remarketing firms may be deemed to be underwriters in connection with their remarketing of offered securities.

Certain agents, underwriters and dealers, and their associates and affiliates, may be customers of, have borrowing relationships with, engage in other transactions with, or perform services, including investment banking services, for us or one or more of our respective affiliates in the ordinary course of business.

In order to facilitate the offering of the securities, any underwriters may engage in transactions that stabilize, maintain or otherwise affect the price of the securities or any other securities the prices of which may be used to determine payments on such securities. Specifically, any underwriters may overallot in connection with the offering, creating a short position for their own accounts. In addition, to cover overallotments or to stabilize the price of the securities or of any such other securities, the underwriters may bid for, and purchase, the securities or any such other securities in the open market. Finally, in any offering of the securities through a syndicate of underwriters, the underwriting syndicate may reclaim selling concessions allowed to an underwriter or a dealer for distributing the securities in the offering if the syndicate repurchases previously distributed securities in transactions to cover syndicate short positions, in stabilization transactions or otherwise. Any of these activities may stabilize or maintain the market price of the securities above independent market levels. Any such underwriters are not required to engage in these activities and may end any of these activities at any time.

We may engage in at the market offerings into an existing trading market in accordance with Rule 415(a)(4) under the Securities Act. In addition, we may enter into derivative transactions with third parties, or sell securities not covered by this prospectus to third parties in privately negotiated transactions. If the applicable prospectus supplement so indicates, in connection with those derivatives, the third parties may sell securities covered by this prospectus and the applicable prospectus supplement, including in short sale transactions. If so, the third party may use securities pledged by us or borrowed from us or others to settle those sales or to close out any related open borrowings of stock, and may use securities received from us in settlement of those derivatives to close out any

related open borrowings of stock. The third party in such sale transactions will be an underwriter and, if not identified in this prospectus, will be named in the applicable prospectus supplement (or a post-effective amendment). In addition, we may otherwise loan or pledge securities to a financial institution or other third party that in turn may sell the securities short using this prospectus and an applicable prospectus supplement. Such financial institution or other third party may transfer its economic short position to investors in our securities or in connection with a concurrent offering of other securities.

Under Rule 15c6-1 of the Exchange Act, trades in the secondary market generally are required to settle in two business days, unless the parties to any such trade expressly agree otherwise. The applicable prospectus supplement may provide that the original issue date for your securities may be more than two scheduled business days after the trade date for your securities. Accordingly, in such a case, if you wish to trade securities on any date prior to the second business day before the original issue date for your securities, you will be required, by virtue of the fact that your securities initially are expected to settle in more than two scheduled business days after the trade date for your securities, to make alternative settlement arrangements to prevent a failed settlement.

The securities may be new issues of securities and may have no established trading market. The securities may or may not be listed on a national securities exchange. We can make no assurance as to the liquidity of or the existence of trading markets for any of the securities.

The specific terms of any lock-up provisions in respect of any given offering will be described in the applicable prospectus supplement.

Any underwriters, dealers and agents may engage in transactions with us, or perform services for us, in the ordinary course of business for which they receive compensation.

The anticipated date of delivery of offered securities will be set forth in the applicable prospectus supplement relating to each offer.

LEGAL MATTERS

Unless the applicable prospectus supplement indicates otherwise, the validity of the securities in respect of which this prospectus is being delivered will be passed upon by Goodwin Procter LLP, Boston, Massachusetts. Any underwriters will also be advised about the validity of the securities and other legal matters by their own counsel, which will be named in the prospectus supplement.

EXPERTS

Ernst & Young LLP, independent registered public accounting firm, has audited our consolidated and combined financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2021, as set forth in their report, which is incorporated by reference in this prospectus and elsewhere in the registration statement. Our financial statements are incorporated by reference in reliance on Ernst & Young LLP's report, given on their authority as experts in accounting and auditing.

WHERE YOU CAN FIND MORE INFORMATION

We file annual, quarterly and current reports, proxy statements and other information with the SEC. Our SEC filings are available to the public over the Internet at the SEC's website at www.sec.gov and on our investor website at www.2seventybio.com. Our website is not a part of this prospectus and is not incorporated by reference in this prospectus.

We have the authority to designate and issue more than one class or series of stock having various preferences, conversion and other rights, voting powers, restrictions, limitations as to dividends, qualifications, and terms and conditions of redemption. See "Description of Capital Stock." We will furnish a full statement of the relative rights and preferences of each class or series of our stock which has been so designated and any restrictions on the ownership or transfer of our stock to any stockholder upon request and without charge. Written requests for such copies should be directed to 60 Binney Street, Cambridge, Massachusetts 02142, Attention: Corporate Secretary.

This prospectus is part of a registration statement on Form S-3 we filed with the SEC. This prospectus omits some information contained in the registration statement in accordance with SEC rules and regulations. You should review the information and exhibits in the registration statement for further information about us and our consolidated subsidiaries and the securities we are offering. Statements in this prospectus concerning any document we filed as an exhibit to the registration statement or that we otherwise filed with the SEC are not intended to be comprehensive and are qualified by reference to these filings. You should review the complete document to evaluate these statements.

INCORPORATION BY REFERENCE

The SEC allows us to incorporate by reference much of the information we file with the SEC, which means that we can disclose important information to you by referring you to those publicly available documents. The information that we incorporate by reference in this prospectus is considered to be part of this prospectus. Because we are incorporating by reference future filings with the SEC, this prospectus is continually updated and those future filings may modify or supersede some of the information included or incorporated in this prospectus. This means that you must look at all of the SEC filings that we incorporate by reference to determine if any of the statements in this prospectus or in any document previously incorporated by reference have been modified or superseded. This prospectus incorporates by reference the documents listed below and any future filings we make with the SEC under Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act, including all filings made after the date of the filing of this registration statement and prior to the effectiveness of this registration statement, except as to any portion of any future report or document that is not deemed filed under such provisions until we sell all of the securities:

- Our Annual Report on Form 10-K for the year ended December 31, 2021, filed on March 22, 2022;
- Our Definitive Proxy Statement on Schedule 14A (to the extent incorporated by reference into our Annual Report on Form 10-K), filed with the SEC on April 26, 2022;
- Our Quarterly Reports on Form 10-Q for the quarters ended March 31, 2022, June 30, 2022 and September 30, 2022, filed with the SEC on May 12, 2022, August 10, 2022 and November 7, 2022, respectively;
- Our Current Reports on Form 8-K filed with the SEC on January 6, 2022, January 11, 2022, March 16, 2022, April 8, 2022, April 29, 2022, June 3, 2022, June 13, 2022, August 10, 2022, September 7, 2022, October 27, 2022 and November 3, 2022 (in each case, except for information contained therein which is furnished rather than filed); and
- The description of our common stock contained in the Information Statement filed with the SEC as Exhibit 99.1 to our Form 10, including any further amendments thereto or reports filed for the purposes of updating such description.

In addition, all reports and other documents filed by us pursuant to the Exchange Act after the date of the initial registration statement and prior to effectiveness of the registration statement shall be deemed to be incorporated by reference into this prospectus.

You may request a copy of these filings, at no cost, by writing or telephoning us at the following address or telephone number:

2seventy bio, Inc.
60 Binney Street, Cambridge, Massachusetts 02142
Attn: Corporate Secretary
617-675-7270

You may also access these documents, free of charge on the SEC's website at *www.sec.gov* or on our website at *www.2seventybio.com*. Information contained on our website is not incorporated by reference into this prospectus, and you should not consider any information on, or that can be accessed from, our website as part of this prospectus or any accompanying prospectus supplement.

Notwithstanding the foregoing, unless specifically stated to the contrary, information that we furnish (and that is not deemed "filed" with the SEC) under Items 2.02 and 7.01 of any Current Report on Form 8-K, including the related exhibits under Item 9.01, is not incorporated by reference into this prospectus or the registration statement of which this prospectus is a part.

This prospectus is part of a registration statement we filed with the SEC. We have incorporated exhibits into this registration statement. You should read the exhibits carefully for provisions that may be important to you.

You should rely only on the information incorporated by reference or provided in this prospectus or any prospectus supplement. We have not authorized anyone to provide you with different information. We are not making an offer of these securities in any state where the offer is not permitted. You should not assume that the information in this prospectus or in the documents incorporated by reference is accurate as of any date other than the date on the front of this prospectus or those documents.

$100,000,000

Common Stock

PROSPECTUS SUPPLEMENT

Joint Book-Running Managers

Goldman Sachs & Co. LLC **Cowen** **SVB Securities**

, 2023