As filed with the Securities and Exchange Commission on October 29, 2025

Registration No. 333-

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

FORM S-3
REGISTRATION STATEMENT
UNDER
THE SECURITIES ACT OF 1933

Summit Therapeutics Inc.
(Exact name of registrant as specified in its charter)

Delaware	**37-1979717**
(State or Other Jurisdiction of Incorporation or Organization)	**(I.R.S. Employer Identification No.)**

601 Brickell Key Drive, Suite 1000
Miami, FL 33131
(305) 203-2034
(Address, including zip code, and telephone number, including area code, of registrant's principal executive offices)

Robert W. Duggan	**Mahkam Zanganeh**
Co-Chief Executive Officer	**Co-Chief Executive Officer**
Summit Therapeutics Inc.	**Summit Therapeutics Inc.**
601 Brickell Key Drive, Suite 1000	**601 Brickell Key Drive, Suite 1000**
Miami, FL 33131	**Miami, FL 33131**
(305) 203-2034	**(305) 203-2034**

(Name, address, including zip code, and telephone number, including area code, of agent for service)

With copies to:

Adam Finerman, Esq.
Baker & Hostetler LLP
45 Rockefeller Plaza
New York, NY 10111
(212) 589-4233

Approximate date of commencement of proposed sale to the public: From time to time after the effective date of this Registration Statement.

If the only securities being registered on this Form are being offered pursuant to dividend or interest reinvestment plans, please check the following box: ☐

If any of the securities being registered on this Form are to be offered on a delayed or continuous basis pursuant to Rule 415 under the Securities Act of 1933, other than securities offered only in connection with dividend or interest reinvestment plans, check the following box: ☒

If this Form is filed to register additional securities for an offering pursuant to Rule 462(b) under the Securities Act, please check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering. ☐

If this Form is a post-effective amendment filed pursuant to Rule 462(c) under the Securities Act, check the following box and list the Securities Act registration statement number of the earlier effective registration statement for the same offering. ☐

If this Form is a registration statement pursuant to General Instruction I.D. or a post-effective amendment thereto that shall become effective upon filing with the Commission pursuant to Rule 462(e) under the Securities Act, check the following box. ☒

If this Form is a post-effective amendment to a registration statement filed pursuant to General Instruction I.D. filed to register additional securities or additional classes of securities pursuant to Rule 413(b) under the Securities Act, check the following box. ☐

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

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

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 7(a)(2)(B) of the Securities Act. ☐

PROSPECTUS

26,682,846 Shares of Common Stock

This prospectus relates to the proposed resale from time to time by the selling stockholders named herein, together with any of such stockholders' transferees, pledgees, donees or successors, an aggregate of 26,682,846 shares (the "Shares") of our common stock, par value $0.01 per share ("common stock"), issued to the selling stockholders pursuant to those certain securities purchase agreements, each dated as of October 21, 2025 (the "Purchase Agreements"), by and among us and the selling stockholders (the "Selling Stockholders").

We are registering the offer and sale of the Shares from time to time by the Selling Stockholders to satisfy registration rights the Selling Stockholders were granted in connection with the Purchase Agreements. We are not selling any of our common stock pursuant to this prospectus, and we will not receive any proceeds from the sale of our common stock offered by this prospectus by the Selling Stockholders.

The Selling Stockholders may offer and sell or otherwise dispose of the Shares described in this prospectus from time to time through public or private transactions at prevailing market prices, at prices related to prevailing market prices or at privately negotiated prices. The Selling Stockholders will bear all underwriting fees, commissions and discounts, if any, attributable to the sales of Shares and any transfer taxes. We will bear all other costs, expenses and fees in connection with the registration of the Shares. See "Plan of Distribution" for more information about how the Selling Stockholders may sell or dispose of the Shares.

Our common stock is listed on The Nasdaq Global Market under the trading symbol "SMMT." On October 28, 2025, the last reported sales price of our common stock on The Nasdaq Global Market was $19.23 per share.

Investing in our common stock involves a high degree of risk. You should review carefully the risks and uncertainties described under the heading "Risk Factors" on page 12 of this prospectus, and under similar headings in any amendment or supplement to this prospectus or in the other documents that are incorporated by reference into this prospectus.

NEITHER THE SECURITIES AND EXCHANGE COMMISSION NOR ANY STATE SECURITIES COMMISSION HAS APPROVED OR DISAPPROVED OF THESE SECURITIES OR DETERMINED IF THIS PROSPECTUS IS TRUTHFUL OR COMPLETE. ANY REPRESENTATION TO THE CONTRARY IS A CRIMINAL OFFENSE.

The date of this prospectus is October 29, 2025

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ABOUT THIS PROSPECTUS

This prospectus is part of an automatically effective registration statement on Form S-3 that we filed with the Securities and Exchange Commission (the "SEC") as a "well-known seasoned issuer" as defined in Rule 405 under the Securities Act of 1933, as amended (the "Securities Act"), using a "shelf" registration process. Under this shelf registration process, the Selling Stockholders may from time to time sell Shares described in this prospectus in one or more offerings or otherwise as described under "Plan of Distribution."

Neither we nor the Selling Stockholders have authorized anyone to provide you with any information other than that contained in, or incorporated by reference into, this prospectus. We take no responsibility for, and can provide no assurance as to the reliability of, any other information that others may give you. This prospectus is an offer to sell only the shares of our common stock offered hereby, but only under circumstances and in jurisdictions where it is lawful to do so. You should not assume that the information contained in or incorporated by reference in this prospectus is accurate as of any date other than their respective dates. Our business, financial condition, results of operations and prospects may have changed since those dates.

This prospectus may be supplemented from time to time by one or more prospectus supplements. Such prospectus supplement may add to, update or change the information contained in this prospectus. If there is any inconsistency between the information in this prospectus and the applicable prospectus supplement, you must rely on the information in the prospectus supplement. You should read both this prospectus and any applicable prospectus supplement together with additional information described below under the heading "Where You Can Find Additional Information."

Throughout this prospectus, when we refer to the Selling Stockholders, we are referring to the Selling Stockholders identified in this prospectus and, as applicable, their permitted transferees or other successors-in-interest that may be identified in a supplement to this prospectus or, if required, a post-effective amendment to the registration statement of which this prospectus is a part.

This prospectus contains summaries of certain provisions contained in some of the documents described herein, but reference is made to the actual documents for complete information. All of the summaries are qualified in their entirety by the actual documents. Copies of some of the documents referred to herein have been filed, will be filed or will be incorporated by reference as exhibits to the registration statement of which this prospectus is a part, and you may obtain copies of those documents as described below under the section titled "Where You Can Find Additional Information."

Unless the context indicates otherwise, as used in this prospectus, the terms "Company," "we," "us," "our," and "Summit," and similar designations, except where context requires otherwise, refer collectively to Summit Therapeutics Inc. and its consolidated subsidiaries.

CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS

This prospectus, each prospectus supplement and the information incorporated by reference in this prospectus and each prospectus supplement contain "forward-looking statements" within the meaning of Section 27A of the Securities Act and Section 21E of the Exchange Act. These forward-looking statements speak only as of the date of this prospectus or the documents incorporated by reference in this prospectus, as applicable, and are subject to a number of risks, uncertainties and assumptions described under the sections in this prospectus and the documents incorporated by reference herein entitled "Risk Factors" and "Management's Discussion and Analysis of Financial Condition and Results of Operations" and elsewhere in this prospectus and the documents incorporated by reference herein.

In some cases, you can identify forward-looking statements by terminology such as "anticipate," "believe," "continue," "could," "estimate," "expect," "forecast," "intends," "may," "might," "plan," "possible," "potential," "predict," "project," "should," "target," "will," "would" or the negative of such terms or other similar expressions. These forward-looking statements are based on our management's current expectations, assumptions, hopes, beliefs, intentions and strategies regarding future events and are based on currently available information as to the outcome and timing of future events. Although we believe such expectations and assumptions to be reasonable, they are inherently uncertain and involve a number of risks and uncertainties that are beyond our control. In addition, management's assumptions about future events may prove to be inaccurate. All readers are cautioned that these forward-looking statements are not guarantees of future performance and we cannot assure any reader that such statements will be realized or that the forward-looking events and circumstances will occur.

Forward-looking statements in this prospectus and the documents incorporated by reference herein include, but are not limited to, statements about:

- the ability to develop a successful product candidate under the License Agreement (as defined below);
- our ability to raise sufficient additional funds to make payments under the License Agreement, and fund ongoing operations and capital needs;
- the timing of and the ability to effectively execute clinical development of ivonescimab;
- the timing, costs, conduct and outcomes of clinical trials for any product candidates, including ivonescimab;
- our plans with respect to possible future collaborations and partnering arrangements;
- the potential benefits of possible future acquisitions or investments in other businesses, products or technologies;
- our plans to pursue research and development of other future product candidates;
- our estimates regarding the potential market opportunity and patient population for commercializing our product candidates, if approved for commercial use;
- our sales, marketing and distribution capabilities and strategy;
- our ability to establish and maintain arrangements with third parties, such as contract research organizations, contract manufacturing organizations, suppliers and distributors;
- the costs and timing of preparing, filing and prosecuting patent applications, maintaining and protecting our intellectual property rights and defending against any intellectual property-related claims;
- our estimates regarding expenses, future revenues, capital requirements and needs for additional financing;
- the impact of government laws and regulations in the United States and in foreign countries;

- the timing and likelihood of regulatory filings and approvals for our product candidates;
- whether regulatory authorities determine that additional trials or data are necessary in order to accept a new drug application for review and/or approval;
- our competitive position;
- our planned use of our existing cash, cash equivalents and short-term investments;
- our ability to attract and retain key scientific or management personnel;
- the impact of public health epidemics, such as the novel coronavirus pandemic ("COVID-19"), natural disasters or geopolitical instability, the response to such events and the potential effects of such events on our business, financial results, supply chain and market;
- the outcome of pending, threatened, and future legal proceedings;
- our expectations regarding the anticipated timeline of our cash, cash equivalents and short-term investments, future financial performance and our ability to continue as a going concern;
- estimates regarding stock-based compensation;
- general economic conditions, including economic slowdowns or other adverse economic conditions, such as periods of increased or prolonged inflation; and
- other risks and uncertainties, including those described under the heading "Risk Factors" included in our most recent Annual Report on Form 10-K for the year ended December 31, 2024, filed with the U.S. Securities and Exchange Commission ("SEC") on February 24, 2025 (the "Annual Report")

Because forward-looking statements are inherently subject to risks and uncertainties, some of which cannot be predicted or quantified and some of which are beyond our control, you should not rely on these forward-looking statements as predictions of future events. The events and circumstances reflected in our forward-looking statements may not be achieved or occur and actual results could differ materially from those projected in the forward-looking statements. Moreover, we operate in an evolving environment. New risk factors and uncertainties may emerge from time to time, and it is not possible for our management to predict all risk factors and uncertainties. Except as required by applicable law, we undertake no obligation to publicly update or revise any forward-looking statements contained herein, whether as a result of any new information, future events, changed circumstances or otherwise. You should, however, review the factors and risks we describe in the reports we will file from time to time with the SEC after the date of this prospectus. See the section entitled "Where You Can Find Additional Information" in this prospectus.

PROSPECTUS SUMMARY

This summary highlights selected information contained elsewhere in this prospectus or incorporated by reference in this prospectus, and does not contain all of the information that you need to consider in making your investment decision. You should carefully read the entire prospectus, including the risks of investing in our securities discussed under the heading "Risk Factors" contained in this prospectus and under similar headings in the other documents that are incorporated by reference into this prospectus. You should also carefully read the information incorporated by reference into this prospectus, including our consolidated financial statements, and the exhibits to the registration statement of which this prospectus is a part.

Company Overview

We are a biopharmaceutical company focused on the discovery, development, and commercialization of patient-, physician-, caregiver- and societal-friendly medicinal therapies intended to improve quality of life, increase potential duration of life, and resolve serious unmet medical needs. Our pipeline of product candidates is designed with the goal to become the patient-friendly, new-era standard-of-care medicines, in the therapeutic area of oncology.

Our current lead development candidate is ivonescimab, a novel, potential first-in-class bispecific antibody intending to combine the effects of immunotherapy via a blockade of PD-1 with the anti-angiogenesis effects of an anti-VEGF compound into a single molecule. On December 5, 2022, we entered into a Collaboration and License Agreement (the "License Agreement") with Akeso, Inc. and its affiliates ("Akeso"), pursuant to which we have in-licensed intellectual property rights related to ivonescimab. Through the License Agreement, we obtained the rights to develop and commercialize ivonescimab in the United States, Canada, Europe, and Japan (the "Initial Licensed Territory"). The License Agreement and transaction closed in January 2023 following customary waiting periods. On June 3, 2024, we entered into an amendment to the License Agreement with Akeso to expand our territories covered under the License Agreement to also include Latin America, including Mexico and all countries in Central America and South America, the Middle East and Africa (together with the Initial Licensed Territory, the "Licensed Territory"). Our operations are focused on the development of ivonescimab and other future activities, as we determine.

We are developing ivonescimab in non-small cell lung cancer ("NSCLC"), specifically conducting Phase III clinical trials in the following proposed indications:

(a) ivonescimab combined with chemotherapy in patients with epidermal growth factor receptor ("EGFR")-mutated, locally advanced or metastatic non-squamous NSCLC who were previously treated with a third-generation EGFR tyrosine kinase inhibitor ("TKI") ("HARMONi");

(b) ivonescimab combined with chemotherapy in patients with first-line metastatic NSCLC ("HARMONi-3"); and

(c) ivonescimab monotherapy in patients with first-line metastatic NSCLC whose tumors have high PD-L1 expression ("HARMONi-7").

In addition, we plan to start developing ivonescimab in colorectal cancer ("CRC") with an intention to begin a Phase III clinical study in the following proposed indication:

(d) ivonescimab combined with chemotherapy in patients with first-line unresectable metastatic CRC ("HARMONi-GI3")

We also intend to expand our ivonescimab clinical development program with an additional set of Phase III clinical studies, with additional color planned to be provided in the first quarter of 2026.

In October 2024, we completed enrollment in our HARMONi clinical trial. In May 2025, we announced topline results from our multiregional, double-blinded, placebo-controlled, Phase III study HARMONi. At the prespecified primary data analysis, ivonescimab in combination with chemotherapy demonstrated a statistically significant improvement in progression free survival (PFS), the magnitude of which we believe to be clinically meaningful, with a hazard ratio of 0.52 (95% CI: 0.41 – 0.66; p<0.00001). PFS was measured by blinded independent central radiology review committee ("BICR") compared to placebo in combination with chemotherapy.

We believe the PFS hazard ratio that was observed in both Asia and ex-Asia sub-populations to be clinically meaningful. The primary analysis demonstrated the consistency of the magnitude of the PFS benefit between patients randomized in Asia and ex-Asia, as well as the consistency in a single-region study (HARMONi-A) with this multiregional study. Ivonescimab in combination with chemotherapy showed a positive trend in overall survival (OS) in the primary analysis without achieving a statistically significant benefit with a hazard ratio of 0.79 (95% CI: 0.62 – 1.01; p=0.057). This trend provides further support for its use in 2L+ EGFRm NSCLC, a setting where high unmet need continues to exist with limited approved options in the United States and other western territories. Currently there are no FDA-approved regimens that have demonstrated a statistically significant overall survival benefit in this patient setting. Both Asian and North American patients demonstrated a positive trend in overall survival. The results of the primary analysis in this multiregional study were consistent with that of the single-region HARMONi-A study, which demonstrated an overall survival hazard ratio of 0.80 at 52% data maturity in a similar patient population.

Overall response rates were higher in the ivonescimab arm (45%) vs. the placebo arm (34%); median duration of response was longer in those patients administered ivonescimab plus chemotherapy (7.6 months) compared to those receiving placebo and chemotherapy (4.2 months).

In September 2025, an additional analysis was performed, whereby the western patients were followed to increase their time on study (Asian patients were locked at the time of the primary analysis). In this analysis that included longer-term follow-up of western patients (median follow-up time of western patients of 13.7 months), a hazard ratio consistent with the primary analysis was observed with an improved nominal p-value (HR=0.78; 95% CI: 0.62 – 0.98; nominal p=0.0332). Median OS for this analysis remained the same in both arms from the primary analysis. Median OS in western patients receiving ivonescimab was 17.0 months compared to 14.0 months for those receiving placebo (HR=0.84); median OS in North American patients, specifically, had not yet been reached in the ivonescimab arm compared to 14.0 months in the placebo arm (HR=0.70). The hazard ratios for western patients in totality, as well as patients from the North American and European regions individually, improved from the primary OS analysis to the analysis with longer-term follow-up of western patients. Consistent benefit was observed across pre-defined subgroups.

In a longer-term follow-up of PFS, which included all western patients and at least six months of follow-up time for all patients, ivonescimab plus chemotherapy demonstrated a consistent improvement in PFS with an observed HR of 0.57 (95% CI: 0.46 – 0.71). With the longer-term follow-up analysis, a consistent benefit in western vs. Asian patients was observed, as well as in patients with tumors with either PD-L1 positive or negative expression. This longer-term follow-up analysis of PFS was performed at the time of the primary OS analysis.

The dual primary endpoints were allocated separate alpha levels and tested individually. The alpha was recycled from the PFS to the OS analysis upon the successful achievement of the PFS endpoint.

Based on the results of the HARMONi clinical trial, we plan to submit a Biologics License Application ("BLA") in order to seek approval for ivonescimab plus chemotherapy for this proposed indication. We intend to submit the BLA in the fourth quarter of 2025. The positive results of the multiregional Phase III study are detailed further under "Product Pipeline" below. As previously noted, the FDA noted that a statistically significant overall

survival benefit is necessary to support marketing authorization in this setting. After careful consideration of the safety and efficacy profile of the current FDA-approved options for patients in this setting, the positive results of the Phase III multiregional study, including regional consistency, as well as discussions with key opinion leaders and those physicians who have administered ivonescimab to patients in a clinical study setting, we believe that the safety and efficacy data generated in the HARMONi study demonstrates that patients suffering from epidermal growth factor receptor (EGFR)-mutant non-small cell lung cancer (NSCLC) in this setting can benefit from the ivonescimab regimen despite the lack of a statistically significant showing on overall survival.

Akeso Collaboration and License Agreement

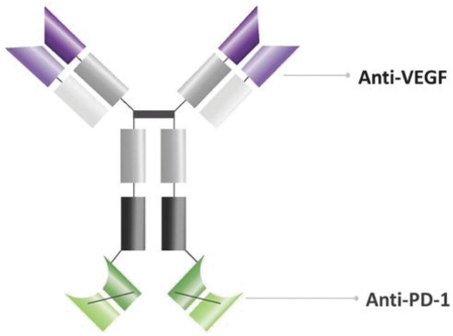
Pursuant to the License Agreement with Akeso, we received the rights to develop and commercialize ivonescimab in the Licensed Territory. Akeso will retain development and commercialization rights for the rest of the world excluding the Licensed Territory. In exchange for these rights, we made an upfront payment during the first quarter of 2023 comprised of $474.9 million cash and the issuance of 10 million shares of our common stock in lieu of $25.1 million cash pursuant to a share transfer agreement. Furthermore, on June 3, 2024, 23 entered into an amendment to the License Agreement with Akeso to expand our territories covered under the License Agreement to also include the Latin America, Middle East and Africa regions for which 23 paid an upfront payment of $15.0 million cash in the third quarter of 2024. In addition, we may also pay Akeso (a) milestone payments tied to achievement of regulatory approval of ivonescimab with various regulatory authorities in the Licensed Territory, (b) milestone payments tied to achievement of annual revenue from ivonescimab in the Licensed Territory and (c) royalty payments equal to low-double-digit percentage of annual revenues from ivonescimab in the Licensed Territory. In connection with the License Agreement, we agreed to purchase a certain portion of drug substance and/or drug product for clinical and commercial supply and to enter into a supply agreement with Akeso.

Pursuant to the terms of the License Agreement, we have final decision-making authority with respect to commercial strategy, pricing and reimbursement and other commercialization matters in the Licensed Territory.

We have not assumed any liabilities (including contingent liabilities), nor acquired any physical assets or trade names, or hired or acquired any employees from Akeso in connection with the License Agreement.

Ivonescimab

Ivonescimab is a novel potential first-in-class PD-1 / VEGF bispecific antibody, believed to be the most advanced in clinical development in the Licensed Territory. Engineered with Akeso's unique Tetrabody technology, ivonescimab, as a single molecule, blocks programmed cell death protein 1 ("PD-1") from binding to PD-L1 and PD-L2, and blocks vascular endothelial growth factor ("VEGF") from binding to VEGF receptors. Ivonescimab is designed to potentially allow cooperative binding of the intended targets, such that the binding of PD-1 increases the binding affinity of VEGF. In view of the co-expression of VEGF and PD-1 in the tumor micro-environment ("TME"), ivonescimab may block these two pathways more effectively and enhance the antitumor activity, as compared to combination therapy through what is believed to be a unique cooperative binding mechanism.



This could differentiate ivonescimab as there is potentially higher expression (presence) of both PD-1 and VEGF in tumor tissue and the TME as compared to normal tissue in the body. As shown in Akeso's *in-vitro* studies, ivonescimab's tetravalent structure (four binding sites) enables higher avidity (accumulated strength of multiple binding interactions) in the TME with over 10 fold increased binding affinity to PD-1 in the presence of VEGF *in vitro*. This tetravalent structure, the intentional novel design of the molecule, and bringing these two targets into a single bispecific antibody with cooperative binding qualities has the potential to direct ivonescimab to the tumor tissue versus healthy tissue. The intent of this design is to improve upon previously established efficacy thresholds, in addition to side effects and safety profiles associated with these targets.

Ivonescimab is currently being developed by both Akeso and us in multiple Phase III clinical trials. There are also multiple early-phase trials being conducted in multiple solid tumors. Ivonescimab has been dosed in more than 3,000 patients globally.

Product Pipeline

Summit Sponsored Ivonescimab Trials

Ivonescimab is currently being investigated in global Phase III clinical trials. Phase I and II trials were completed by or are ongoing with our partner Akeso. This pipeline reflects Phase III clinical trials that have been or are planned to be initiated by us in our Licensed Territory.

Indication	Study	Treatment Population	Regimen
NSCLC	HARMONi	2L+ EGFRm+	+ Chemo vs. chemo
	HARMONi-3	1L	+ Chemo vs. pembrolizumab (PD-1) + chemo
	HARMONi-7	1L PD-L1 high	Monotherapy vs. pembrolizumab (PD-1)
CRC	HARMONi-GI3	1L CRC	ivonescimab + FOLFOX vs. bevacizumab + FOLFOX

HARMONi

HARMONi study (NCT05184712) is a Phase III, multi-regional, potentially registration-enabling clinical trial, which enrolled patients in North America, Europe, and China. Patients enrolled in China were also enrolled

as a part of the HARMONi-A study. We completed enrollment of patients in North America and Europe in October 2024. The two primary endpoints for this study are PFS and OS, and the study compares ivonescimab plus platinum-based doublet chemotherapy versus placebo plus platinum-based doublet chemotherapy in patients with advanced or metastatic EGFR-mutated NSCLC whose tumors have progressed following treatment with a third generation EGFR-TKI.

In May 2025, we announced topline results from our multiregional, double-blinded, placebo-controlled, Phase III study HARMONi. At the prespecified primary data analysis, ivonescimab in combination with chemotherapy demonstrated a statistically significant improvement in PFS, the magnitude of which we believe to be clinically meaningful, with a hazard ratio of 0.52 (95% CI: 0.41 – 0.66; p<0.00001); median PFS was 6.8 months for those patients receiving ivonescimab plus chemotherapy compared to 4.4 months for those receiving chemotherapy. PFS was measured by blinded independent central radiology review committee ("BICR") compared to placebo in combination with chemotherapy.

We believe the PFS hazard ratio that was observed in both Asia and ex-Asia sub-populations to be clinically meaningful. The primary analysis demonstrated the consistency of the magnitude of the PFS benefit between patients randomized in Asia and ex-Asia, as well as the consistency in a single-region study (HARMONi-A) with this multiregional study. Ivonescimab in combination with chemotherapy showed a positive trend in overall survival (OS) in the primary analysis without achieving a statistically significant benefit with a hazard ratio of 0.79 (95% CI: 0.62 – 1.01; p=0.057). This trend provides further support for its use in 2L+ EGFRm NSCLC, a setting where high unmet need continues to exist with limited approved options in the United States and other western territories. Currently there are no FDA-approved regimens that have demonstrated a statistically significant overall survival benefit in this patient setting. Both Asian and North American patients demonstrated a positive trend in overall survival. The results of the primary analysis in this multiregional study were consistent with that of the single-region HARMONi-A study, which demonstrated an overall survival hazard ratio of 0.80 at 52% data maturity in a similar patient population.

Overall response rates were higher in the ivonescimab arm (45%) vs. the placebo arm (34%); median duration of response was longer in those patients administered ivonescimab plus chemotherapy (7.6 months) compared to those receiving placebo and chemotherapy (4.2 months).

In September 2025, an additional analysis was performed, whereby the western patients were followed to increase their time on study (Asian patients were locked at the time of the primary analysis). In this analysis that included longer-term follow-up of western patients (median follow-up time of western patients of 13.7 months), a hazard ratio consistent with the primary analysis was observed with an improved nominal p-value (HR=0.78; 95% CI: 0.62 – 0.98; nominal p=0.0332). Median OS for this analysis remained the same in both arms from the primary analysis. Median OS in western patients receiving ivonescimab was 17.0 months compared to 14.0 months for those receiving placebo (HR=0.84); median OS in North American patients, specifically, had not yet been reached in the ivonescimab arm compared to 14.0 months in the placebo arm (HR=0.70). The hazard ratios for western patients in totality, as well as patients from the North American and European regions individually, improved from the primary OS analysis to the analysis with longer-term follow-up of western patients. Consistent benefit was observed across pre-defined subgroups.

In a longer-term follow-up of PFS, which included all western patients and at least six months of follow-up time for all patients, ivonescimab plus chemotherapy demonstrated a consistent improvement in PFS with an observed HR of 0.57 (95% CI: 0.46 – 0.71). With the longer-term follow-up analysis, a consistent benefit in western vs. Asian patients was observed, as well as in patients with tumors with either PD-L1 positive or negative expression. This longer-term follow-up analysis of PFS was performed at the time of the primary OS analysis.

The dual primary endpoints were allocated separate alpha levels and tested individually. The alpha was recycled from the PFS to the OS analysis upon the successful achievement of the PFS endpoint.

The safety profile of ivonescimab in combination with chemotherapy was acceptable and manageable in the context of the observed clinical benefit with comparable rates of discontinuation and death between both arms. There were 16 patients (7.3%) who discontinued ivonescimab due to treatment-related adverse events (TRAEs) compared to 11 patients (5.0%) who discontinued placebo due to TRAEs. There were four patients (1.8%) in the ivonescimab plus chemotherapy arm and five patients (2.3%) in the chemotherapy alone arm who died as a result of TRAEs. In the ivonescimab plus chemotherapy arm, 50.0% of patients experienced Grade 3 or higher TRAEs compared to 42.2% in the chemotherapy arm. Of note, 0.9% of patients in the ivonescimab plus chemotherapy arm experienced Grade 3 or higher hemorrhage (bleeding) events. Based on the results of the HARMONi clinical trial, we plan to submit a BLA in order to seek approval for ivonescimab plus chemotherapy in this setting.

HARMONi-3

HARMONi-3 study (NCT05899608) is a Phase III, multi-regional, potentially registration-enabling clinical trial for which we initiated activating sites in North America and China during the fourth quarter of 2023 and later in Europe in 2024. The two primary endpoints for this study are PFS and OS, and the study compares ivonescimab plus platinum-based doublet chemotherapy versus pembrolizumab plus platinum-based doublet chemotherapy in first-line patients with metastatic squamous NSCLC and non-squamous NSCLC. Enrollment is ongoing in all regions for patients with squamous tumors; the protocol amendment is effective and enrollment began in the United States in the fourth quarter of 2024 for patients with non-squamous tumors.

In October 2025, we announced a protocol amendment to separate the statistical analysis of the primary endpoints by histology. Therefore, there will be separate analyses conducted to evaluate ivonescimab plus chemotherapy compared to pembrolizumab plus chemotherapy in patients with squamous NSCLC and in patients with non-squamous NSCLC.

As a result of having two separate intention-to-treat analyses within the HARMONi-3 study, the analyses for squamous tumors and non-squamous tumors may be conducted at separate times, as each analysis will be conducted upon the prespecified numbers of events being reached in the separate cohorts.

Enrollment in the squamous cohort of HARMONi-3 is expected to complete in the first half of 2026. We expect to reach the prespecified number of events for the PFS primary endpoint analysis for this cohort in the second half of 2026. An interim analysis for overall survival may be conducted at a similar time.

Enrollment in the non-squamous cohort of HARMONi-3 is expected to complete in the second half of 2026. We expect to reach the prespecified number of events for the PFS primary endpoint analysis for this cohort in the first half of 2027. An interim analysis for overall survival is planned to be conducted based upon reaching a prespecified number of events.

In order to sufficiently power for PFS and OS in both cohorts of this study, we plan to enroll 600 patients with squamous NSCLC and 1,000 patients with non-squamous NSCLC.

HARMONi-7

Based on the results of HARMONi-2, we are enrolling in the HARMONi-7 study (NCT06767514). HARMONi-7 is a multi-regional, potentially registration-enabling Phase III clinical trial that will compare ivonescimab monotherapy to pembrolizumab monotherapy in patients with metastatic squamous and non-squamous NSCLC whose tumors have high PD-L1 expression. The sample size for this study is currently planned to have an estimated 780 patients with two primary endpoints, PFS and OS.

HARMONi-GI3

In October 2025, we announced we intend to start HARMONi-GI3, a Phase III, multi-regional, clinical trial evaluating ivonescimab plus chemotherapy compared to bevacizumab plus chemotherapy as first line therapy in patients with unresectable metastatic colorectal cancer (CRC). The primary endpoint for this study is PFS and we plan to enroll 600 patients. Clinical trial sites for HARMONi-GI3 are planned to begin activating in the United Stated prior to the end of the year

Potential Future Clinical Development and Additional Current Activities

We are conducting our current clinical trials, and plan to design and conduct additional clinical trial activities for ivonescimab within the Licensed Territory, to support and submit relevant regulatory filings. We intend to explore further clinical development of ivonescimab in solid tumor settings outside of metastatic NSCLC and metastatic CRC, our current areas of focus in its Phase III clinical trials.

In the fourth quarter of 2023, we began collaborating with multiple institutions globally and opened our investigator- sponsored trials program across several disease areas. We continued to expand this program in 2024 in order to discover additional opportunities for ivonescimab, including in several tumors outside of our current development plan.

We plan to review the data generated from these clinical trials as a part of our consideration for advancing our clinical development pipeline for ivonescimab in the Licensed Territory.

Additional Ivonescimab Development: Akeso-Sponsored Trials

Akeso is currently developing ivonescimab in NSCLC and other solid tumor settings. Ivonescimab is currently approved in China in combination with chemotherapy for patients with EGFR-mutated NSCLC whose tumors have progressed following an EGFR-TKI based on the results of the HARMONi-A clinical trial that was first announced and presented in 2024. In addition, a supplemental application was submitted in China by Akeso for ivonescimab as monotherapy based on the results of the HARMONi-2 study in first-line, PD-L1 positive NSCLC, and was approved by the National Medical Products Administration (“NMPA”) in April 2025 for this indication as well. Also in April 2025, Akeso announced positive results for the HARMONi-6 study in first-line squamous NSCLC. Further details related to these three trials, in addition to other Phase II clinical data presented during 2024, are described further below. Akeso is currently conducting Phase III clinical trials in combination with chemotherapy in first-line biliary tract cancer (“HARMONi-GI1”), in first-line advanced PD-L1 low or negative triple-negative breast cancer (“HARMONi-BC1”), in first-line advanced microsatellite stable colorectal cancer (“HARMONi-GI3”) and in NSCLC for patients whose tumors have progressed following PD-(L)1 inhibitor based therapy (“HARMONi-8A”), as well as in combination with ligufalimab, a proprietary Akeso-owned investigational CD-47 monoclonal antibody, in first-line recurrent / metastatic PD-L1 positive head-and-neck cancer (“HARMONi-HN1”) and in combination with ligufalimab plus chemotherapy in first-line advanced pancreatic cancer (“HARMONi-GI2”).

HARMONi-A

Based on data published by Akeso at the American Society of Clinical Oncology (“ASCO 2024”) and in a publication in the Journal of the American Medical Association (JAMA) in the HARMONi-A study, in a single-region (China), randomized, double-blinded Phase III study in patients with NSCLC who have progressed following an EGFR-TKI, ivonescimab achieved its primary endpoint of PFS when combined with doublet chemotherapy (pemetrexed and carboplatin). Patients experienced a 54% reduction in disease progression or death as compared to placebo plus doublet-chemotherapy (HR: 0.46, 95% CI: 0.34 - 0.62; $p<0.001$). In a

pre-specified subgroup analysis of patients who received a previous third-generation TKI, a hazard ratio of 0.48 was observed. A median Overall Survival ("mOS") in this study of 17.1 months was observed, reflecting a 20% reduction in death as compared to placebo plus chemotherapy in the study (HR: 0.80, 95% CI: 0.59 - 1.08). The Phase III study was considered to have demonstrated a tolerable safety profile and a low discontinuation rate for adverse events.

In August 2025, Akeso announced that in the final OS analysis of HARMONi-A, ivonescimab met the OS clinical endpoint, demonstrating a statistically significant and clinically meaningful OS benefit. As the first Phase III final analysis for ivonescimab, these results not only reinforce its breakthrough value in PFS, but also highlight its ability to deliver significant OS improvement, a key endpoint in global oncology drug development.

HARMONi-2

After announcing positive qualitative results for the HARMONi-2 trial, also referred to as AK112-303, a randomized, single-region (China) Phase III study sponsored by Akeso, on May 30, 2024, we announced, on September 8, 2024, quantitative data from the primary analysis of the Phase III HARMONi-2 trial featuring ivonescimab that was presented as part of the Presidential Symposium at the International Association for the Study of Lung Cancer's ("IASLC") 2024 World Conference on Lung Cancer ("WCLC 2024"). The HARMONi-2 presentation evaluated monotherapy ivonescimab compared to monotherapy pembrolizumab in patients with locally advanced or metastatic NSCLC whose tumors have positive PD-L1 expression. HARMONi-2 is a single region, multi-center, double-blinded Phase III study conducted in China sponsored by Akeso, with all relevant data exclusively generated, managed, and analyzed by Akeso.

In the HARMONi-2 primary analysis, ivonescimab monotherapy demonstrated a statistically significant improvement in the trial's primary endpoint, PFS by Independent Radiologic Review Committee ("IRRC"), when compared to monotherapy pembrolizumab, achieving a hazard ratio of 0.51 (95% CI: 0.38, 0.69; $p<0.0001$). A clinically meaningful benefit was demonstrated across clinical subgroups, including patients with tumors with high PD-L1 expression. OS data was not yet mature at the time of the data cutoff of the primary analysis.

Ivonescimab demonstrated an acceptable and manageable safety profile, which was consistent with previous studies. There were three patients (1.5%) who discontinued ivonescimab due to treatment-related adverse events ("TRAEs") compared to six patients (3.0%) who discontinued pembrolizumab due to TRAEs. There was one patient in the ivonescimab arm and two patients in the pembrolizumab arm who died as a result of TRAEs in this Phase III study.

On April 25, 2025, Akeso announced that ivonescimab was approved in China by the NMPA, the Chinese Health Authority, for a second indication based on the results of the HARMONi-2 trial. As a part of the review of the supplemental marketing application submitted by Akeso seeking a label expansion of ivonescimab in China, the NMPA requested that Akeso perform an interim analysis of OS. Akeso announced that the results of this interim overall survival analysis included a clinically meaningful hazard ratio of 0.777. The analysis was conducted at 39% data maturity, with a nominal alpha level of 0.0001.

HARMONi-6

After announcing positive qualitative results for the HARMONi-6 trial, on April 23, 2025, detailed clinical trial results of the study were presented as part of the Presidential Symposium at the European Society for Medical Oncology's 2025 Congress ("ESMO 2025"). The HARMONi-6 study evaluated ivonescimab in combination with platinum-based chemotherapy compared to tislelizumab (a PD-1 inhibitor) in combination with platinum-based chemotherapy in patients with previously untreated advanced NSCLC irrespective of PD-L1 expression.

HARMONi-6, also referred to as AK112-306, is a single region, multi-center, double-blinded Phase III study conducted in China sponsored by Akeso, with all relevant data exclusively generated, managed, and analyzed by Akeso.

In the HARMONi-6 planned PFS interim analysis, ivonescimab in combination with chemotherapy demonstrated a statistically significant improvement in the primary endpoint, PFS, by IRRC, when compared to tislelizumab in combination with chemotherapy, achieving a hazard ratio of 0.60 (95% CI: 0.46, 0.78; p<0.0001). A clinically meaningful benefit was demonstrated across clinical subgroups, including those with either PD-L1 negative or positive expression, as well as high-risk patients. OS data was not yet mature at the time of the data cutoff and will be evaluated in the future.

Ivonescimab demonstrated an acceptable and manageable safety profile in the HARMONi-6 study, which was consistent with previous blinded Phase III studies conducted studying ivonescimab. Nine patients (3.4%) discontinued ivonescimab plus chemotherapy due to treatment-related adverse events (TRAEs) compared to 11 patients (4.2%) receiving tislelizumab plus chemotherapy due to TRAEs. There were eight patients in the ivonescimab plus chemotherapy arm and 10 patients in the tislelizumab plus chemotherapy arm who died as a result of TRAEs in this Phase III study.

Additional Phase II Data Sets

In addition to the HARMONi-2 data announced at WCLC 2024, Akeso also announced Phase II trial results from AK112-205, for patients with Stage II or III resectable NSCLC. Further, we announced data for ivonescimab was presented as a part of the 2024 European Society for Medical Oncology Annual Congress (“ESMO 2024”) featuring updated Phase II ivonescimab data in advanced triple-negative breast cancer (“TNBC”), recurrent / metastatic head and neck squamous cell carcinoma (“HNSCC”), and metastatic microsatellite-stable (“MSS”) colorectal cancer (“CRC”). At ASCO 2024, Akeso presented ivonescimab Phase II data in biliary-tract cancer (“BTC”). Earlier, at the 2024 European Lung Cancer Conference (“ELCC 2024”), Akeso announced updated data from AK112-201 (Cohort 1), a Phase II study for patients with first-line advanced NSCLC. Each trial from which the data was generated was a multi-center Phase II study conducted in China sponsored by Akeso, with data generated and analyzed by Akeso.

Recent Developments

Private Placement

On October 21, 2025, we entered into the Purchase Agreements with multiple leading biotech institutional and individual accredited investors (the “Investors”), for the sale by us in a private placement (the “Private Placement”) of an aggregate of 26,682,846 shares (the “Shares”) of our common stock, at purchase price of $18.74 per Share, which was the closing price of the common stock on October 21, 2025, for aggregate gross proceeds to us of approximately $500.0 million (the “Private Placement”). The closing of the Private Placement occurred on or about October 24, 2025. The proceeds of the Private Placement are expected to be used to advance, in part, the clinical development of ivonescimab, in addition to working capital needs and general corporate purposes.

Robert W. Duggan, our Co-Chief Executive Officer, Executive Chairman of our Board of Directors (the “Board”) and majority stockholder, Dr. Mahkam Zanganeh, Co-Chief Executive Officer, President and member of the Board, Manmeet Soni, Chief Operating Officer, Chief Financial Officer and member of the Board, Bhaskar Anand, Chief Accounting Officer, and certain non-executive employees and other related persons each participated as Investors in the Private Placement, purchasing an aggregate of 14,477,049 shares of Common Stock. Additionally, Akeso, Inc. (“Akeso”), participated as an Investor in the Private Placement, purchasing

533,617 shares of Common Stock. Dr. Yu (Michelle) Xia, a member of the Board, is the Chief Executive Officer and Chairwoman of Akeso.

The offer and sale of shares of common stock issued to the Investors were not initially registered under the Securities Act or any state securities laws. We relied on the exemption from the registration requirements afforded by Section 4(a)(2) of the Securities Act and/or Regulation D promulgated thereunder for the Private Placement. In connection with their execution of the respective Purchase Agreements, each of the Investors represented to us that such Investor is either (i) an "accredited investor" as defined in Regulation D of the Securities Act, or (ii) a qualified institutional buyer (as defined in Rule 144A of the Securities Act), and that the securities purchased by such Investor were being acquired solely for its own account and for investment purposes and not with a present view to its future public sale or distribution.

On October 21, 2025, in connection with the Purchase Agreements, we entered into Registration Rights Agreements with the Investors (the "Registration Rights Agreements"). The Registration Rights Agreements provide, among other things, that we will as soon as reasonably practicable, and in any event by no later than December 19, 2025, file with the Securities and Exchange Commission (the "SEC") a registration statement registering the resale of the Shares. We agreed to use our reasonable best efforts to have such registration statement declared effective as soon as practicable after the filing thereof. The registration statement to which this prospectus forms a part is intended to satisfy such requirements under the Registration Rights Agreements.

Corporate Information

Summit Therapeutics Inc. was incorporated in Delaware on July 17, 2020. Our principal executive office is located at 601 Brickell Key Drive, Suite 1000, Miami, FL 33131 and our phone number is (305) 203-2034. Our website is https://www.smmttx.com. Information contained on or accessible through our website is not incorporated by reference into this prospectus and should not be considered a part of this prospectus. We have included our website in this prospectus solely as an inactive textual reference.

This prospectus contains references to our trademarks and to trademarks belonging to other entities. Solely for convenience, trademarks and trade names referred to in this prospectus, including logos, artwork and other visual displays, may appear without the ® or ™ symbols, but such references are not intended to indicate, in any way, that their respective owners will not assert, to the fullest extent under applicable law, their rights thereto. We do not intend our use or display of other companies' trade names or trademarks to imply a relationship with, or endorsement or sponsorship of us by, any other companies.

THE OFFERING	
Common stock offered by the Selling Stockholders	26,682,846 shares.
Use of Proceeds	We will not receive any proceeds from the sale of the Shares covered by this prospectus. See “Use of Proceeds.”
Risk Factors	An investment in our common stock involves a high degree of risk. See “Risk Factors” on page 11 of this prospectus, and under similar headings in the other documents that are incorporated by reference into this prospectus for a discussion of the factors you should consider before deciding to invest in shares of our common stock.
Nasdaq Global Market symbol	SMMT

RISK FACTORS

Investing in our common stock involves a high degree of risk. Before deciding whether to invest in our common stock, you should consider carefully the risks and uncertainties described under the heading “Risk Factors” contained in our most recent Annual Report on Form 10-K, as updated and supplemented by subsequent Quarterly Reports on Form 10-Q and Current Reports on Form 8-K that we have filed with the SEC, and by our other filings we make with the SEC which are incorporated by reference into this prospectus, together with other information in this prospectus and the documents incorporated by reference into this prospectus. The risks described in these documents are not the only ones we face, but those that we consider to be material. Additional risks not presently known to us or that we currently deem immaterial may also impair our business operations. 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 common stock could decline due to the materialization of any of these risks and you may lose all or part of your investment.

For more information about our SEC filings, please see “Where You Can Find More Information” and “Incorporation of Certain Information by Reference.”

USE OF PROCEEDS

We are registering the resale of the Shares by the Selling Stockholders. We will not receive any proceeds from the sale or other disposition of the Shares offered by this prospectus.

The Selling Stockholders will bear all fees, commissions and discounts, if any, attributable to the sale of the Shares. We will bear all other costs, expenses and fees in connection with the registration of the Shares to be sold by the Selling Stockholders pursuant to this prospectus.

SELLING STOCKHOLDERS

We have prepared this prospectus to allow the Selling Stockholders to offer and sell from time to time up to 26,682,846 Shares. We are registering the offer and sale of the Shares to satisfy certain registration obligations that we granted the Selling Stockholders in the Private Placement.

The following table sets forth (i) the name of each Selling Stockholder; (ii) the number of shares of common stock beneficially owned by each Selling Stockholder; (iii) the number of Shares that may be offered under this prospectus; and (iv) the number of shares of common stock beneficially owned by each Selling Stockholder assuming all of the Shares covered hereby are sold. We do not know how long the Selling Stockholders will hold the Shares before selling them. We currently have no agreements, arrangements or understandings with the Selling Stockholders regarding the sale or other disposition of any Shares. Other than as set forth below, the Selling Stockholders do not have, or within the past three years has not had, any material relationship with us or any of our or affiliates.

Beneficial ownership is determined in accordance with the rules of the SEC and includes voting or investment power with respect to our common stock. Generally, a person "beneficially owns" shares of common stock if the person has or shares with others the right to vote those shares or to dispose of them, or if the person has the right to acquire voting or disposition rights within 60 days.

The information set forth in the table below is based upon information obtained from the Selling Stockholders. The percentage of shares beneficially owned prior to, and after, the offering is based on 771,150,384 shares of our common stock outstanding as of October 24, 2025, after giving effect to the closing of the Private Placement, and assumes the Selling Stockholders dispose of all of the Shares covered by this prospectus and do not acquire beneficial ownership of any additional shares of common stock. The registration of the Shares does not necessarily mean that the Selling Stockholders will sell all or any portion of the Shares covered by this prospectus.

As used in this prospectus, the term "Selling Stockholders" includes the Selling Stockholders listed in the table below, together with any additional Selling Stockholders listed in a prospectus supplement, and their donees, pledgees, assignees, transferees, distributees and successors-in-interest that receive Shares in any non-sale transfer after the date of this prospectus. Unless otherwise noted below, the address for the Selling Stockholders is 601 Brickell Key Drive, Suite 1000, Miami, FL 33131.

	Shares of Common Stock beneficially owned before this offering		Shares of Common Stock offered pursuant to this prospectus	Shares of Common Stock beneficially owned after this offering(2)	
Name of Selling Stockholder	Number of shares	Percentage of outstanding shares	Number of shares (1)	Number of shares	Percentage of shares
Baker Bros. Advisors LP (3)	36,391,063	4.7%	2,668,089	33,722,974	4.4%
Fidelity Select Portfolios: Pharmaceuticals Portfolio (4)	262,104	*	188,587	73,517	*
Fidelity Select Portfolios: Biotechnology Portfolio(4)	1,757,991	*	400,213	1,357,778	*
Fidelity Contrafund: Fidelity Contrafund K6 (4)	553,212	*	477,612	75,600	*
Fidelity Contrafund: Fidelity Series Opportunistic Insights Fund (4)	131,362	*	104,262	27,100	*
Fidelity Insights Investment Trust (4)	159,190	*	126,260	32,930	*
Fidelity US Equity Mother Fund (4)	43,718	*	33,518	10,200	*
Fidelity Global Growth and Value Investment Trust (4)	14,673	*	11,228	3,445	*

Name of Selling Stockholder	Shares of Common Stock beneficially owned before this offering		Shares of Common Stock offered pursuant to this prospectus	Shares of Common Stock beneficially owned after this offering(2)	
	Number of shares	Percentage of outstanding shares	Number of shares (1)	Number of shares	Percentage of shares
Fidelity Contrafund Commingled Pool (4)	967,140	*	835,576	131,564	*
Fidelity Contrafund: Fidelity Advisor New Insights Fund (4)	254,151	*	204,246	49,905	*
Variable Insurance Products Fund II: VIP Contrafund Portfolio (4)	285,884	*	228,195	57,689	*
Fidelity Contrafund: Fidelity Contrafund (4)	2,602,618	*	2,248,185	354,433	*
T. Rowe Price Health Sciences Fund, Inc. (5)	6,650,198	*	3,510,505	3,139,693	*
TD Mutual Funds – TD Health Sciences Fund (5)	538,781	*	284,986	253,795	*
T. Rowe Price Health Sciences Portfolio (5)	393,050	*	206,643	186,407	*
Akeso, Inc. (6)	32,057,147	4.2%	533,617	31,523,530	4.1%
James Warren Huff (7)	203,361	*	53,361	150,000	*
Brad Hughes (8)	78,994	*	53,361	25,633	*
Robert W. Duggan (9)	570,081,922	73.9%	13,980,789	556,101,133	72.1%
Mahkam Zanganeh (10)	54,756,617	6.9%	266,808	54,489,809	6.9%
Manmeet S. Soni (11)	21,010,922	2.7%	53,361	20,957,561	2.7%
Bhaskar Anand (12)	309,751	*	26,680	283,071	*
Mahshad Zanganeh (13)	76,680	*	26,680	50,000	*
Eric Clow (14)	9,762,354	1.3%	96,051	9,666,303	1.2%
Susan Kim (15)	53,231	*	5,336	47,895	*
Pawan Parihar (16)	108,817	*	10,672	98,145	*
Urte Gayko (17)	6,077,020	*	5,336	6,071,684	*
Dsara Duggan (18)	89,966	*	37,353	52,613	*
Dave Gancarz (19)	6,397,439	*	5,336	6,392,103	*

* Less than one percent (1%)

(1) Represents all of the Shares that each Selling Stockholder may offer and sell from time to time under this prospectus.

(2) Assumes each Selling Stockholder sells the maximum number of Shares possible in this offering.

(3) Consists of (i) 3,064,563 shares of common stock held directly by 667, L.P. (“667”) and (ii) 33,326,500 shares of common stock held directly by Baker Brothers Life Sciences, L.P. (“Life Sciences”, and together with 667, the “BBA Funds”). Shares offered pursuant to this prospectus consists of (i) 220,832 shares of common stock purchased by 667 in the Private Placement and (ii) 2,447,257 shares of common stock purchased by Life Sciences in the Private Placement. Baker Bros. Advisors LP (“BBA”) is the investment adviser to the BBA Funds and has the sole voting and investment power with respect to the securities held by the BBA Funds and thus may be deemed to beneficially own such securities. Baker Bros. Advisors (GP) LLC (“BBA GP”) is the sole general partner of BBA and thus may be deemed to beneficially own the securities held by the BBA Funds. The managing members of BBA GP are Julian C. Baker and Felix J. Baker, who may be deemed to beneficially own the securities held by the BBA Funds. Julian C. Baker, Felix J. Baker, BBA and BBA GP disclaim beneficial ownership of all shares held by the BBA Funds, except to the extent of their indirect pecuniary interest therein. The business address of BBA, BBA GP, Julian C. Baker and Felix J. Baker is 860 Washington Street, 3rd Floor, New York, NY 10014.

(4) Shares offered pursuant to this prospectus consists of: (i) 188,587 shares of common stock purchased in the Private Placement by Fidelity Select Portfolios: Pharmaceuticals Portfolio; (ii) 400,213 shares of common stock purchased in the Private Placement by Fidelity Select Portfolios: Biotechnology Portfolio; (iii) 477,612 shares of common stock purchased in the Private Placement by Fidelity Contrafund: Fidelity Contrafund K6; (iv) 104,262 shares of common stock purchased in the Private Placement by Fidelity Contrafund: Fidelity Series Opportunistic Insights Fund; (v) 126,260 shares of common stock purchased in the Private Placement by Fidelity Insights Investment Trust; (vi) 33,518 shares of common stock purchased in the Private Placement by Fidelity US Equity Mother Fund; (vii) 11,228 shares of common stock purchased in the Private Placement by Fidelity Global Growth and Value Investment Trust; (viii) 835,576 shares of common stock purchased in the Private Placement by Fidelity Contrafund Commingled Pool; (ix) 204,246 shares of common stock purchased in the Private Placement by Fidelity Contrafund: Fidelity Advisor New Insights Fund; (x) 228,195 shares of common stock purchased in the Private Placement by Variable Insurance Products Fund II: VIP Contrafund Portfolio; and (xi) 2,248,185 shares of common stock purchased in the Private Placement by Fidelity Contrafund: Fidelity Contrafund. These funds and accounts are managed by direct or indirect subsidiaries of FMR LLC. Abigail P. Johnson is a Director, the Chairman and the Chief Executive Officer of FMR LLC. Members of the Johnson family, including Abigail P. Johnson, are the predominant owners, directly or through trusts, of Series B voting common shares of FMR LLC, representing 49% of the voting power of FMR LLC. The Johnson family group and all other Series B shareholders have entered into a shareholders' voting agreement under which all Series B voting common shares will be voted in accordance with the majority vote of Series B voting common shares. Accordingly, through their ownership of voting common shares and the execution of the shareholders' voting agreement, members of the Johnson family may be deemed, under the Investment Company Act of 1940, to form a controlling group with respect to FMR LLC. The address of these funds and accounts is 245 Summer Street, Boston, MA 02210.

(5) Shares offered pursuant to this prospectus consists of: (i) 3,510,505 shares of common stock purchased in the Private Placement by T. Rowe Price Health Sciences Fund, Inc., (ii) 284,986 shares of common stock purchased in the Private Placement by TD Mutual Funds—TD Health Sciences Fund and (iii) 206,643 shares of common stock purchased in the Private Placement by T. Rowe Price Health Sciences Portfolio. These funds and accounts are advised or subadvised by T. Rowe Price Associates, Inc. ("TRPA"). TRPA, as investment adviser, has dispositive and voting power with respect to the securities held by these funds and accounts. TRPA may be deemed to be the beneficial owner of these securities, however, TRPA expressly disclaims that it is, in fact, the beneficial owner of such securities. TRPA is a wholly owned subsidiary of T. Rowe Price Group, Inc., which is a publicly traded financial services holding company. The principal business address of the selling stockholders is T. Rowe Price Associates, Inc., 100 East Pratt Street, Baltimore, MD 21202.

(6) Shares beneficially owned prior to the offering to which this prospectus relates consists of 32,057,147 shares of common stock held directly by Akeso, Inc. ("Akeso"). Shares offered pursuant to this prospectus consists of 533,617 shares of common stock purchased in the Private Placement by Akeso. Dr. Michelle Xia, a member of our Board of Directors, is a stockholder, serves as chairwoman, president and chief executive officer of Akeso, and exercises the right to vote approximately 25.96% of Akeso's ordinary shares based on a Form 4 filed by Dr. Xia on October 23, 2025. Dr. Xia disclaims beneficial ownership of all shares of common stock held by Akeso, except to the extent of her pecuniary interest therein. The address of this selling stockholder is Floor 4, Willow House, Cricket Square, Grand Cayman KY1-9010, Cayman Islands.

(7) Shares offered pursuant to this prospectus consists of 53,361 shares of common stock purchased in the Private Placement by Mr. Huff.

(8) Shares offered pursuant to this prospectus consists of 53,361 shares of common stock purchased in the Private Placement by Mr. Hughes.

(9) Shares beneficially owned prior to the offering to which this prospectus relates is based upon a Schedule 13D/A filed by Mr. Duggan with the Securities and Exchange Commission on September 13, 2024, updated by Form 4s filed by Mr. Duggan on January 6, 2025, April 9, 2025, May 1, 2025, June 2, 2025, September 11, 2025 and October 23, 2025, and information known to the Company, and consists of (i) 570,073,879 shares of common stock owned directly by Mr. Duggan and (ii) 8,043 shares of common stock

issuable pursuant to outstanding options that are exercisable within 60 days of October 24, 2025. Shares offered pursuant to this prospectus consists of 13,980,789 shares of common stock purchased in the Private Placement by Mr. Duggan. Mr. Duggan serves as the Company's Co-Chief Executive Officer and Executive Chairman. The number of shares of common stock beneficially owned by Mr. Duggan reported in the table above does not include the 54,756,617 shares of common stock which are beneficially owned by Mr. Duggan's spouse, Dr. Zanganeh, and which are described in footnote 10 below. As spouses, Mr. Duggan and Dr. Zanganeh may be deemed to have acquired beneficial ownership of the securities held by the other spouse upon their marriage on December 18, 2024. Mr. Duggan does not hold any voting or investment power over such securities held by Dr. Zanganeh. Mr. Duggan disclaims beneficial ownership of such securities, except to the extent of his pecuniary interest therein.

(10) Shares beneficially owned prior to the offering to which this prospectus relates is based upon a Schedule 13D/A filed by Dr. Zanganeh with the Securities and Exchange Commission on March 13, 2023, updated by Form 4s filed by Dr. Zanganeh on January 6, 2025, April 9, 2025, May 1, 2025, June 2, 2025, September 11, 2025 and October 23, 2025. The shares of common stock beneficially owned consist of (i) 31,000 shares of common stock owned directly by Dr. Zanganeh, (ii) 25,724,474 shares of common stock owned by the Mahkam Zanganeh Revocable Trust, (iii) 10,199,776 shares of common stock owned by the Shaun Zanganeh Irrevocable Trust, (iv) 18,724,687 shares of common stock issuable pursuant to outstanding options that are exercisable within 60 days of October 24, 2025, and (v) 76,680 shares purchased by an immediate family member (which are also described in footnote 13). Shares offered pursuant to this prospectus consists of 266,808 shares of common stock purchased in the Private Placement by the Mahkam Zanganeh Revocable Trust. Dr. Zanganeh is the trustee of each of the Mahkam Zanganeh Revocable Trust and the Shaun Zanganeh Irrevocable Trust. Dr. Zanganeh serves as the Company's Co-Chief Executive Officer, President and member of the Company's Board of Directors. The number of shares of common stock beneficially owned by Dr. Zanganeh as reported in the table above does not include the 570,081,922 shares of common stock which are beneficially owned by Dr. Zanganeh's spouse, Mr. Duggan, and which are described in footnote 9 above. As spouses, Dr. Zanganeh and Mr. Duggan may be deemed to have acquired beneficial ownership of the securities held by the other spouse upon their marriage on December 18, 2024. Dr. Zanganeh does not hold any voting or investment power over such securities held by Mr. Duggan. Dr. Zanganeh disclaims beneficial ownership of all such securities, except to the extent of her pecuniary interest therein.

(11) Shares beneficially owned prior to the offering to which this prospectus relates is based upon Form 4s filed by Mr. Soni with the Securities and Exchange Commission on August 23, 2024, September 13, 2024, May 1, 2025 and October 23, 2025, and information known to the Company. The shares of common stock beneficially owned consists of (i) 3,073,603 shares of common stock owned by Mr. Soni and (ii) 17,937,319 shares of common stock issuable pursuant to outstanding options that are exercisable within 60 days of October 24, 2025. Shares offered pursuant to this prospectus consists of 53,361 shares of common stock purchased in the Private Placement by Mr. Soni. Mr. Soni serves as the Company's Chief Financial Officer, Chief Operating Officer and member of the Company's Board of Directors.

(12) Shares beneficially owned prior to the offering to which this prospectus relates is based upon the Form 4s by Mr. Anand on September 13, 2024, January 14, 2025, May 1, 2025, September 19, 2025 and October 23, 2025, and information known to the Company. The shares of common stock beneficially owned consists of (i) 159,751 shares owned by Mr. Anand and (ii) 150,000 shares of common stock issuable pursuant to outstanding options that are exercisable within 60 days of October 24, 2025. Shares offered pursuant to this prospectus consists of 26,680 shares of common stock purchased in the Private Placement by Mr. Anand. Mr. Anand serves as Chief Accounting Officer of the Company.

(13) Shares beneficially owned prior to the offering to which this prospectus relates consists of 76,680 shares held by Ms. Mahshad Zanganeh. Shares offered pursuant to this prospectus consists of 26,680 shares of common stock purchased in the Private Placement by Ms. Mahshad Zanganeh. Ms. Mahshad Zanganeh is the sister of Dr. Mahkam Zanganeh, our Co-Chief Executive Officer, President and member of our Board of Directors.

(14) Shares beneficially owned prior to the offering to which this prospectus relates consists of (i) 228,611 shares of common stock owned directly by Mr. Clow, (ii) 1,915,415 shares of common stock held by Mr. Clow's

spouse, Fong Clow, (iii) 1,288,938 shares of common stock jointly owned by Mr. Clow and Fong Clow, and (iv) 6,329,390 shares of common stock issuable pursuant to outstanding options held by Fong Clow that are exercisable within 60 days of October 24, 2025. Mr. Clow may be deemed to beneficially own the shares of common stock held by Fong Clow. Fong Clow is our Chief Biometrics Officer. Shares offered pursuant to this prospectus consists of 96,051 shares of common stock purchased in the Private Placement by Mr. Clow.

(15) Shares beneficially owned prior to the offering to which this prospectus relates consists of (i) 6,981 shares owned by Ms. Kim and (ii) 46,250 shares of common stock issuable pursuant to outstanding options that are exercisable within 60 days of October 24, 2025. Shares offered pursuant to this prospectus consists of 5,336 shares of common stock purchased in the Private Placement by Ms. Kim. Ms. Kim serves as our Vice President, Legal.

(16) Shares beneficially owned prior to the offering to which this prospectus relates consists of (i) 83,817 shares owned by Mr. Parihar and (ii) 25,000 shares of common stock issuable pursuant to outstanding options that are exercisable within 60 days of October 24, 2025. Shares offered pursuant to this prospectus consists of 10,672 shares of common stock purchased in the Private Placement by Mr. Parihar. Mr. Parihar serves as our Head of IT and Facilities.

(17) Shares beneficially owned prior to the offering to which this prospectus relates consists of (i) 118,034 shares owned by Dr. Gayko and (ii) 5,958,986 shares of common stock issuable pursuant to outstanding options that are exercisable within 60 days of October 24, 2025. Shares offered pursuant to this prospectus consists of 5,336 shares of common stock purchased in the Private Placement by Dr. Gayko. Dr. Gayko serves as our Chief Regulatory, Quality and Pharmacovigilance Officer.

(18) Shares beneficially owned prior to the offering to which this prospectus relates consists of 89,966 shares owned by the Catherine Zwan TR UA 11/9/2012 Dsara Ann Duggan Trust of which Ms. Duggan is the beneficiary. Shares offered pursuant to this prospectus consists of 37,353 shares of common stock purchased in the Private Placement by the Catherine Zwan TR UA 11/9/2012 Dsara Ann Duggan Trust. Ms. Duggan is the daughter of Mr. Duggan, our Co-Chief Executive Officer and Executive Chairman.

(19) Shares beneficially owned prior to the offering to which this prospectus relates consists of (i) 91,364 shares owned by Mr. Gancarz and (ii) 6,306,075 shares of common stock issuable pursuant to outstanding options that are exercisable within 60 days of October 24, 2025. Shares offered pursuant to this prospectus consists of 5,336 shares of common stock purchased in the Private Placement by Mr. Gancarz. Mr. Gancarz serves as our Chief Business & Strategy Officer.

PLAN OF DISTRIBUTION

We are registering the resale of the shares of our common stock held by the Selling Stockholders from time to time after the date of this prospectus. We will not receive any of the proceeds from the sale by the Selling Stockholders of the shares of our common stock. The Selling Stockholders will bear all fees, commissions and discounts, if any, attributable to the sales of shares and any transfer taxes. We will bear all other costs, expenses and fees in connection with the registration of shares of our common stock to be sold by the Selling stockholders pursuant to this prospectus.

The term "Selling Stockholders" includes donees, pledgees, transferees or other successors in interest selling securities received after the date of this prospectus from the Selling Stockholders as a gift, pledge, partnership distribution or other transfer. The Selling Stockholders will act independently of us in making decisions with respect to the timing, manner and size of each sale. Such sales may be made on the principal trading market for our common stock or any other stock exchange, market or trading facility on which our common stock is traded or in private transactions. These sales may be at fixed or negotiated prices. The Selling Stockholders may use any one or more of the following methods when selling securities:

- ordinary brokerage transactions and transactions in which the broker dealer solicits purchasers;
- block trades in which the broker dealer will attempt to sell the common stock as agent but may position and resell a portion of the block as principal to facilitate the transaction;
- purchases by a broker dealer as principal and resale by the broker dealer for its account;
- an exchange distribution in accordance with the rules of the applicable exchange;
- directly to one or more purchasers;
- settlement of short sales;
- distribution to employees, members, limited partners or stockholders of the Selling Stockholders;
- in transactions through broker dealers that agree with the Selling Stockholders to sell a specified number of such common stock at a stipulated price per security;
- through the writing or settlement of options or other hedging transactions, whether through an options exchange or otherwise;
- by pledge to secured debts and other obligations;
- delayed delivery arrangements;
- to or through underwriters, broker-dealers or agents; provided that in no event shall any resales by the Selling Stockholders take the form of an underwritten offering (as the term "underwritten public offering" is commonly understood, which for clarity does not include a transaction that does not involve the purchase by such broker-dealer of securities with a view to public resale thereby, but which transaction may be treated similarly to an underwritten public offering in terms of the procedures to be followed thereby as a matter of law or customary practice) without our prior consent;
- in "at the market" offerings, as defined in Rule 415 under the Securities Act, at negotiated prices, at prices prevailing at the time of sale or at prices related to such prevailing market prices, including sales made directly on a national securities exchange or sales made through a market maker other than on an exchange or other similar offerings through sales agents;
- in privately negotiated transactions;
- in options transactions;
- a combination of any such methods of sale; or
- any other method permitted pursuant to applicable law.

The Selling Stockholders may also sell the shares of our common stock under Rule 144 or any other exemption from registration under the Securities Act, if available, rather than under this prospectus.

In addition, each Selling Stockholders that is an entity may elect to make a pro rata in-kind distribution of securities to its members, partners or stockholders pursuant to the registration statement of which this prospectus is a part by delivering a prospectus with a plan of distribution. Such members, partners or stockholders would thereby receive freely tradeable securities pursuant to the distribution through a registration statement. To the extent a distributee is our affiliate (or to the extent otherwise required by law), we may, at our option, file a prospectus supplement in order to permit the distributees to use the prospectus to resell the securities acquired in the distribution.

Broker-dealers engaged by the Selling Stockholders may arrange for other brokers-dealers to participate in sales. Broker-dealers may receive commissions or discounts from the selling stockholder (or, if any broker-dealer acts as agent for the purchaser of our common stock, from the purchaser) in amounts to be negotiated, but, except as set forth in a supplement to this prospectus, in the case of an agency transaction not in excess of a customary brokerage commission in compliance with Financial Industry Regulatory Authority, or FINRA, Rule 5110; and in the case of a principal transaction a markup or markdown in compliance with FINRA Rule 2121.

To the extent required, this prospectus may be amended or supplemented from time to time to describe a specific plan of distribution. In connection with the sale of our common stock or interests therein, the Selling Stockholders may enter into hedging transactions with broker-dealers or other financial institutions, which may in turn engage in short sales of our common stock in the course of hedging the positions they assume. The Selling Stockholders may also sell our common stock short and deliver these shares to close out their short positions, or loan or pledge the securities to broker-dealers that in turn may sell these shares. The Selling Stockholders may also enter into option or other transactions with broker-dealers or other financial institutions or create one or more derivative securities which require the delivery to such broker-dealer or other financial institution of securities offered by this prospectus, which securities such broker-dealer or other financial institution may resell pursuant to this prospectus (as supplemented or amended to reflect such transaction). The Selling Stockholders may also pledge securities to a broker-dealer or other financial institution, and, upon a default, such broker-dealer or other financial institution, may effect sales of the pledged securities pursuant to this prospectus (as supplemented or amended to reflect such transaction).

In effecting sales, broker-dealers or agents engaged by the Selling Stockholders may arrange for other broker-dealers to participate. Broker-dealers or agents may receive commissions, discounts or concessions from the Selling Stockholders in amounts to be negotiated immediately prior to the sale.

The Selling Stockholders have informed us that they do not have any written or oral agreement or understanding, directly or indirectly, with any person to distribute the shares of our common stock.

We will pay certain fees and expenses incurred by us incident to the registration of the resale of the Shares. We have agreed to indemnify the selling stockholder against certain losses, claims, damages and liabilities, including liabilities under the Securities Act, and the Selling Stockholders may be entitled to contribution. We may be indemnified by the Selling Stockholders against certain losses, claims, damages and liabilities, including liabilities under the Securities Act that may arise from any written information furnished to us by the Selling Stockholders specifically for use in this prospectus, or we may be entitled to contribution.

The resale securities will be sold only through registered or licensed brokers or dealers if required under applicable state securities laws. In addition, in certain states, the resale securities covered hereby may not be sold unless they have been registered or qualified for sale in the applicable state or an exemption from the registration or qualification requirement is available and is complied with.

Under applicable rules and regulations under the Exchange Act, any person engaged in the distribution of the resale shares of our common stock may not simultaneously engage in market making activities with respect to

our common stock for the applicable restricted period, as defined in Regulation M, prior to the commencement of the distribution. In addition, the Selling Stockholders will be subject to applicable provisions of the Exchange Act and the rules and regulations thereunder, including Regulation M, which may limit the timing of purchases and sales of our common stock by the Selling Stockholders or any other person. We will make copies of this prospectus available to the Selling Stockholders and have informed them of the need to deliver a copy of this prospectus to each purchaser at or prior to the time of the sale (including by compliance with Rule 172 under the Securities Act).

At the time a particular offer of securities is made, if required, a prospectus supplement will be distributed that will set forth the number of securities being offered and the terms of the offering, including the name of any underwriter, dealer or agent, the purchase price paid by any underwriter, any discount, commission and other item constituting compensation, any discount, commission or concession allowed or reallowed or paid to any dealer, and the proposed selling price to the public.

We have agreed with the Selling Stockholders to keep the registration statement of which this prospectus forms a part effective until the earlier of (i) the date on which the Selling Stockholders cease to hold any Shares issued pursuant to Purchase Agreement, and (iii) all the Shares held by the Selling Stockholders may be sold without registration under Rule 144 and without being subject to any volume, manner of sale or publicly available information requirements.

LEGAL MATTERS

Baker & Hostetler LLP, New York, New York, will pass upon the validity of the shares of our common stock offered by this prospectus.

EXPERTS

The financial statements and management's assessment of the effectiveness of internal control over financial reporting (which is included in Management's Report on Internal Control over Financial Reporting) incorporated in this prospectus by reference to the Annual Report on Form 10-K for the year ended December 31, 2024 have been so incorporated in reliance on the report (which contains an explanatory paragraph relating to the Company's net losses from operations and cash outflows from operating activities as described in Note 3 to the financial statements) of PricewaterhouseCoopers LLP, an independent registered public accounting firm, given on the authority of said firm as experts in auditing and accounting.

WHERE YOU CAN FIND MORE INFORMATION

We file annual, quarterly and other 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. Our Annual Report on Form 10-K, Quarterly Reports on Form 10-Q, and Current Reports on Form 8-K, including any amendments to those reports, and other information that we file with or furnish to the SEC pursuant to Section 13(a) or 15(d) of the Exchange Act can also be accessed free of charge through the Internet. These filings will be available as soon as reasonably practicable after we electronically file such material with, or furnish it to, the SEC.

This prospectus is part of a registration statement that 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 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 OF CERTAIN INFORMATION BY REFERENCE

The SEC allows us to incorporate by reference the information and reports we file with it, which means that we can disclose important information to you by referring you to these documents. The information incorporated by reference is an important part of this prospectus, and information that we file after the date hereof with the SEC will automatically update and supersede the information already incorporated by reference. We are incorporating by reference the documents listed below:

- Our Annual Report on Form 10-K for the fiscal year ended December 31, 2024, as filed on February 24, 2025;
- The information specifically incorporated by reference into our Annual Report on Form 10-K for the fiscal year ended December 31, 2024 from our Definitive Proxy Statement on Schedule 14A (other than information furnished rather than filed), filed on April 29, 2025;
- Our Quarterly Reports on Form 10-Q for the quarters ended March 31, 2025, as filed on May 1, 2025, June 30, 2025, as filed on August 11, 2025, and September 30, 2025, as filed on October 20, 2025;
- Our Current Reports on Form 8-K filed on January 24, 2025, April 23, 2025, April 25, 2025, May 30, 2025, June 17, 2025, June 20, 2025, August 11, 2025, September 8, 2025, October 20, 2025 and October 22, 2025; and
- The description of our Common Stock which is registered under Section 12 of the Exchange Act, in our registration statement on Form 8-A, filed on September 18, 2020, including any amendment or report filed for the purpose of updating such description.

All documents we file with the SEC pursuant to Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act shall be deemed incorporated by reference in this prospectus and to be a part of this prospectus from the date of filing of those documents, with the exception of any portion of any report or document that is not deemed "filed" under such provisions on or after the date of this prospectus, until the earlier of the date on which: (1) all of the securities, the offer and resale of which are registered hereunder, have been sold; or (2) the registration statement of which this prospectus is a part has been withdrawn.

Under no circumstances will any information filed under current items 2.02 or 7.01 of Form 8-K be deemed incorporated herein by reference unless such Form 8-K expressly provides to the contrary.

Upon written or oral request, we will provide without charge to each person to whom a copy of the prospectus is delivered a copy of the documents incorporated by reference herein (other than exhibits to such documents unless such exhibits are specifically incorporated by reference herein). You may request a copy of these filings, at no cost, by writing, calling or emailing us at the contact information set forth below. We have authorized no one to provide you with any information that differs from that contained in this prospectus. Accordingly, we take no responsibility for any other information that others may give you. You should not assume that the information in this prospectus is accurate as of any date other than the date of the front cover of this prospectus

Summit Therapeutics Inc.
601 Brickell Key Drive, Suite 1000
Miami, FL 33131
Attention: Investor Relations
(305) 203-2034

PART II
INFORMATION NOT REQUIRED IN THE PROSPECTUS

Item 14. Other Expenses of Issuance and Distribution.

The following table sets forth an estimate of the fees and expenses payable by us in connection with the issuance and distribution of the securities being registered (other than the underwriting discounts and commissions and expenses incurred by the Selling Stockholders in disposing of its Shares). All the amounts shown are estimates, except for the SEC registration fee.

	Amount
SEC registration fee	$ 69,387
Legal fees and expenses	15,000
Accounting fees and expenses	25,000
Miscellaneous fees and expenses	10,000
Total	$ 119,387

Item 15. Indemnification of Directors and Officers.

Section 145(a) of the DGCL provides, in general, that a corporation may indemnify any person who was or is a party to or is threatened to be made a party to any threatened, pending or completed action, suit or proceeding, whether civil, criminal, administrative or investigative (other than an action by or in the right of the corporation), because he or she is or was a director, officer, employee or agent of the corporation, or is or was serving at the request of the corporation as a director, officer, employee or agent of another corporation, partnership, joint venture, trust or other enterprise, against expenses (including attorneys' fees), judgments, fines and amounts paid in settlement actually and reasonably incurred by the person in connection with such action, suit or proceeding, if he or she acted in good faith and in a manner he or she reasonably believed to be in or not opposed to the best interests of the corporation and, with respect to any criminal action or proceeding, had no reasonable cause to believe his or her conduct was unlawful.

Section 145(b) of the DGCL provides, in general, that a corporation may indemnify any person who was or is a party or is threatened to be made a party to any threatened, pending or completed action or suit by or in the right of the corporation to procure a judgment in its favor because the person is or was a director, officer, employee or agent of the corporation, or is or was serving at the request of the corporation as a director, officer, employee or agent of another corporation, partnership, joint venture, trust or other enterprise, against expenses (including attorneys' fees) actually and reasonably incurred by the person in connection with the defense or settlement of such action or suit if he or she acted in good faith and in a manner he or she reasonably believed to be in or not opposed to the best interests of the corporation, except that no indemnification shall be made with respect to any claim, issue or matter as to which he or she shall have been adjudged to be liable to the corporation unless and only to the extent that the Court of Chancery or other adjudicating court determines that, despite the adjudication of liability but in view of all of the circumstances of the case, he or she is fairly and reasonably entitled to indemnity for such expenses that the Court of Chancery or other adjudicating court shall deem proper.

Section 145(g) of the DGCL provides, in general, that a corporation may purchase and maintain insurance on behalf of any person who is or was a director, officer, employee or agent of the corporation, or is or was serving at the request of the corporation as a director, officer, employee or agent of another corporation, partnership, joint venture, trust or other enterprise, against any liability asserted against such person and incurred by such person in any such capacity, or arising out of his or her status as such, whether or not the corporation would have the power to indemnify the person against such liability under Section 145 of the DGCL.

The registrant's Certificate of Incorporation provides that the registrant will indemnify each person who was or is a party or threatened to be made a party to or is involved in any threatened, pending or completed action, suit or

proceeding, whether civil, criminal, administrative or investigative (other than an action by or in the right of the registrant) by reason of the fact that he or she is or was a director or officer of the registrant, or is or was serving at the registrant's request as a director or officer of another corporation, partnership, joint venture, trust or other enterprise to the fullest extent permitted by the DGCL. The registrant's Certificate of Incorporation provides that any reasonable, documented, out-pocket expenses must be advanced to these indemnitees under certain circumstances.

The indemnification provisions contained in the registrant's Certificate of Incorporation are not exclusive. In addition, the registrant has entered into indemnification agreements with each of its directors and executive officers. Each indemnification agreement provides that the registrant will indemnify the director or executive officer to the fullest extent permitted by law for claims arising in his or her capacity as a director or executive officer, provided that he or she acted in good faith and in a manner that he or she reasonably believed to be in, or not opposed to, the registrant's best interests and, with respect to any criminal proceeding, had no reasonable cause to believe that his or her conduct was unlawful. In the event that the registrant does not assume the defense of a claim against a director or executive officer, the registrant is required to advance his or her expenses in connection with his defense, provided that he or she undertakes to repay all amounts advanced if it is ultimately determined that he or she is not entitled to be indemnified by the registrant.

In addition, the registrant maintains standard policies of insurance under which coverage is provided to the registrant's directors and officers against losses arising from claims made by reason of breach of duty or other wrongful act, and to the registrant with respect to payments which may be made by the registrant to such directors and officers pursuant to the above indemnification provisions or otherwise as a matter of law.

Item 16. Exhibits.

Exhibit No.	Description
3.1	Restated Certificate of Incorporation of the Registrant (incorporated by reference to Exhibit 3.1 to the Registrant's Current Report on Form 8-K (File No. 001-36866), filed with the Securities and Exchange Commission on September 18, 2020)
3.2	Amendment to Restated Certificate of Incorporation of the Registrant (incorporated by reference to Exhibit 3.1 to the Registrant's Current Report on Form 8-K (File No. 001-36866), filed with the Securities and Exchange Commission on July 29, 2022)
3.3	Amendment No. 2 to Restated Certificate of Incorporation (incorporated by reference to Exhibit 5.1 to Registrant's Current Report on Form 8-K (File No. 001-36866), filed with the Securities and Exchange Commission on January 20, 2023)
3.4	Amended and Restated Bylaws (incorporated by reference to Exhibit 3.2 to the Registrant's Current Report on Form 8-K (File No. 001-36866), filed with the Securities and Exchange Commission on September 18, 2020)
5.1*	Opinion of Baker & Hostetler LLP
23.1*	Consent of PricewaterhouseCoopers LLP, an independent registered public accounting firm for the Registrant
23.2*	Consent of Baker & Hostetler LLP (included in Exhibit 5.1)
24.1*	Powers of Attorney (included on signature page hereto)
107*	Filing Fee Table

* Filed herewith.

Item 17. Undertakings.

(a) The undersigned registrant hereby undertakes:

(1) To file, during any period in which offers or sales are being made, a post-effective amendment to this registration statement:

(i) To include any prospectus required by Section 10(a)(3) of the Securities Act of 1933;

(ii) To reflect in the prospectus any facts or events arising after the effective date of the registration statement (or the most recent post-effective amendment thereof) which, individually or in the aggregate, represent a fundamental change in the information set forth in the registration statement. Notwithstanding the foregoing, any increase or decrease in volume of securities offered (if the total dollar value of securities offered would not exceed that which was registered) and any deviation from the low or high end of the estimated maximum offering range may be reflected in the form of prospectus filed with the SEC pursuant to Rule 424(b) if, in the aggregate, the changes in volume and price represent no more than a 20% change in the maximum aggregate offering price set forth in the "Calculation of Registration Fee" table in the effective registration statement; and

(iii) To include any material information with respect to the plan of distribution not previously disclosed in the registration statement or any material change to such information in the registration statement;

provided, however, that paragraphs (a)(1)(i), (a)(1)(ii) and (a)(1)(iii) do not apply if the information required to be included in a post-effective amendment by those paragraphs is contained in reports filed with or

furnished to the SEC by the registrant pursuant to Section 13 or Section 15(d) of the Securities Exchange Act of 1934 that are incorporated by reference in the registration statement, or is contained in a form of prospectus filed pursuant to Rule 424(b) that is part of the registration statement;

(2) That, for the purpose of determining any liability under the Securities Act of 1933, each such post-effective amendment shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time shall be deemed to be the initial bona fide offering thereof.

(3) To remove from registration by means of a post-effective amendment any of the securities being registered which remain unsold at the termination of the offering.

(4) That, for the purpose of determining liability under the Securities Act of 1933 to any purchaser:

(i) Each prospectus filed by the registrant pursuant to Rule 424(b)(3) shall be deemed to be part of the registration statement as of the date the filed prospectus was deemed part of and included in the registration statement; and

(ii) Each prospectus required to be filed pursuant to Rule 424(b)(2), (b)(5), or (b)(7) as part of a registration statement in reliance on Rule 430B relating to an offering made pursuant to Rule 415(a)(1)(i), (vii), or (x) for the purpose of providing the information required by Section 10(a) of the Securities Act of 1933 shall be deemed to be part of and included in the registration statement as of the earlier of the date such form of prospectus is first used after effectiveness or the date of the first contract of sale of securities in the offering described in the prospectus. As provided in Rule 430B, for liability purposes of the issuer and any person that is at that date an underwriter, such date shall be deemed to be a new effective date of the registration statement relating to the securities in the registration statement to which that prospectus relates, and the offering of such securities at that time shall be deemed to be the initial bona fide offering thereof. Provided, however, that no statement made in a registration statement or prospectus that is part of the registration statement or made in a document incorporated or deemed incorporated by reference into the registration statement or prospectus that is part of the registration statement will, as to a purchaser with a time of contract of sale prior to such effective date, supersede or modify any statement that was made in the registration statement or prospectus that was part of the registration statement or made in any such document immediately prior to such effective date.

(b) The undersigned registrant hereby undertakes that, for purposes of determining any liability under the Securities Act of 1933, each filing of the registrant's annual report pursuant to section 13(a) or section 15(d) of the Securities Exchange Act of 1934 (and, where applicable, each filing of an employee benefit plan's annual report pursuant to section 15(d) of the Securities Exchange Act of 1934) that is incorporated by reference in the registration statement shall be deemed to be a new registration statement relating to the securities offered therein, and the offering of such securities at that time shall be deemed to be the initial bona fide offering thereof.

(c) Insofar as indemnification for liabilities arising under the Securities Act of 1933 may be permitted to directors, officers and controlling persons of the registrant pursuant to the foregoing provisions, or otherwise, the registrant has been advised that in the opinion of the Securities and Exchange Commission such indemnification is against public policy as expressed in the Securities Act of 1933 and is, therefore, unenforceable. In the event that a claim for indemnification against such liabilities (other than the payment by the registrant of expenses incurred or paid by a director, officer or controlling person of the registrant in the successful defense of any action, suit or proceeding) is asserted by such director, officer or controlling person in connection with the securities being registered, the registrant will, unless in the opinion of its counsel the matter has been settled by controlling precedent, submit to a court of appropriate jurisdiction the question whether such indemnification by it is against public policy as expressed in the Securities Act of 1933 and will be governed by the final adjudication of such issue.

SIGNATURES

Pursuant to the requirements of the Securities Act of 1933, the registrant certifies that it has reasonable grounds to believe that it meets all of the requirements for filing on Form S-3 and has duly caused this registration statement to be signed on its behalf by the undersigned, thereunto duly authorized, in the City of Miami, State of Florida, on October 29, 2025.

SUMMIT THERAPEUTICS INC.

By: /s/ Robert W. Duggan
Robert W. Duggan
Co-Chief Executive Officer and Executive Chairman
(Principal Executive Officer)

By: /s/ Mahkam Zanganeh
Dr. Mahkam Zanganeh
Co-Chief Executive Officer, President and Director
(Principal Executive Officer)

POWER OF ATTORNEY

KNOW ALL PERSONS BY THESE PRESENTS, that each person whose signature appears below hereby constitutes and appoints Robert W. Duggan, Dr. Mahkam Zanganeh and Manmeet Soni, and each of them singly, as the undersigned's true and lawful attorneys-in-fact and agents, with full power of substitution, for the undersigned in any and all capacities, to sign any or all amendments to this Registration Statement (including post-effective amendments), and to file the same, with all exhibits thereto, and other documents in connection therewith, with the Securities and Exchange Commission, granting unto said attorneys-in-fact and agents full power and authority to do and perform each and every act and thing requisite and necessary to be done in connection therewith, as fully for all intents and purposes as the undersigned might or could do in person, hereby and about the premises hereby ratifying and confirming all that said attorneys-in-fact and agent, proxy and agent, or their substitute, may lawfully do or cause to be done by virtue hereof.

Pursuant to the requirements of the Securities Act of 1933, this registration statement has been signed below by the following persons in the capacities and on the dates indicated.

Name	Title	Date
/s/ Robert W. Duggan Robert W. Duggan	Co-Chief Executive Officer and Executive Chairman *(Principal Executive Officer)*	October 29, 2025
/s/ Mahkam Zanganeh Dr. Mahkam Zanganeh	Co-Chief Executive Officer, President and Director *(Principal Executive Officer)*	October 29, 2025
/s/ Manmeet S. Soni Manmeet S. Soni	Chief Operating Officer, Chief Financial Officer and Director *(Principal Financial Officer)*	October 29, 2025
/s/ Bhaskar Anand Bhaskar Anand	Head of Finance and Chief Accounting Officer *(Principal Accounting Officer)*	October 29, 2025

Name	Title	Date
/s/ Robert Booth Dr. Robert Booth	Director	October 29, 2025
/s/ Alessandra Cesano Dr. Alessandra Cesano	Director	October 29, 2025
/s/ Kenneth Clark Kenneth Clark	Director	October 29, 2025
/s/ Jeff Huber Jeff Huber	Director	October 29, 2025
/s/ Mostafa Ronaghi Dr. Mostafa Ronaghi	Director	October 29, 2025
/s/ Yu Xia Dr. Yu Xia	Director	October 29, 2025

BakerHostetler

Baker&Hostetler LLP
45 Rockefeller Plaza
New York, NY 10111

T 212.589.4200
F 212.589.4201
www.bakerlaw.com

October 29, 2025

Summit Therapeutics Inc.
601 Brickell Key Drive, Suite 1000
Miami, FL 33131

Ladies and Gentlemen:

We have acted as counsel to Summit Therapeutics Inc., a Delaware corporation (the "**Company**"), in connection with the filing of the Company's Registration Statement on Form S-3 (the "**Registration Statement**") with the Securities and Exchange Commission (the "**Commission**") under the Securities Act of 1933, as amended (the "**Act**"), covering the registration for resale of up to an aggregate of 26,682,846 shares (the "**Shares**") of the Company's common stock, par value $0.01 per share (the "**Common Stock**"), held by the selling stockholders identified in the Registration Statement.

We have examined such documents and such matters of fact and law as we deem necessary to render the opinion contained herein. In our examination, we have assumed, but have not independently verified, the genuineness of all signatures, the conformity to original documents of all documents submitted to us as certified facsimile or other copies, and the authenticity of all such documents. As to questions of fact material to this opinion, we have relied on certificates or comparable documents of public officials and of officers and representatives of the Company.

Based on such examination, we are of the opinion that the Shares are validly issued, fully paid and nonassessable.

The opinion expressed herein is limited to the General Corporation Law of the State of Delaware and we express no opinion as to the effect on the matters covered by this letter of the laws of any other jurisdiction.

We hereby consent to the filing of this letter as Exhibit 5.1 to the Registration Statement and to the reference to our firm under the heading "Legal Matters" in the prospectus included in the Registration Statement. In giving such consent, we do not hereby admit that we are in the category of persons whose consent is required under Section 7 of the Act or the rules and regulations of the Commission.

Very truly yours,

/s/ Baker & Hostetler LLP

BAKER & HOSTETLER LLP

Exhibit 23.1

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We hereby consent to the incorporation by reference in this Registration Statement on Form S-3 of Summit Therapeutics Inc. of our report dated February 24, 2025 relating to the financial statements and the effectiveness of internal control over financial reporting, which appears in Summit Therapeutics Inc.'s Annual Report on Form 10-K for the year ended December 31, 2024. We also consent to the reference to us under the heading "Experts" in such Registration Statement.

/s/ PricewaterhouseCoopers LLP

San Jose, California
October 29, 2025

Calculation of Filing Fee Tables

S-3

Summit Therapeutics Inc.

Table 1: Newly Registered and Carry Forward Securities ☐Not Applicable

		Security Type	Security Class Title	Fee Calculation or Carry Forward Rule	Amount Registered	Proposed Maximum Offering Price Per Unit	Maximum Aggregate Offering Price	Fee Rate	Amount of Registration Fee	Carry Forward Form Type	Carry Forward File Number	Carry Forward Initial Effective Date	Filing Fee Previously Paid in Connection with Unsold Securities to be Carried Forward
Newly Registered Securities													
Fees to be Paid	1	Equity	Common Stock, par value $0.01 per share	Other	26,682,846	$ 18.83	$ 502,437,990.18	0.0001381	$ 69,386.69				
Fees Previously Paid													
Carry Forward Securities													
Carry Forward Securities													
					Total Offering Amounts:		$ 502,437,990.18		$ 69,386.69				
					Total Fees Previously Paid:				$ 0.00				
					Total Fee Offsets:				$ 0.00				
					Net Fee Due:				$ 69,386.69				

Offering Note

[1] (1) The shares of common stock, par value $0.01 per share ("Common Stock"), of the Registrant will be offered for resale by the selling stockholders. Pursuant to Rule 416 under the Securities Act of 1933, as amended (the "Securities Act"), the shares being registered hereunder include such indeterminate number of shares of Common Stock as may be issuable with respect to the shares being registered hereunder as a result of stock splits, stock dividends or similar transactions. (2) Estimated solely for the purpose of calculating the amount of the registration fee pursuant to Rule 457(c) of the Securities Act. The proposed maximum offering price per share and maximum aggregate offering price are calculated using the average of the high ($19.20) and low ($18.46) prices of the Common Stock as reported on the Nasdaq Global Market on October 23, 2025, which date is within five business days prior to the filing of this registration statement.

Table 2: Fee Offset Claims and Sources ☑Not Applicable

		Registrant or Filer Name	Form or Filing Type	File Number	Initial Filing Date	Filing Date	Fee Offset Claimed	Security Type Associated with Fee Offset Claimed	Security Title Associated with Fee Offset Claimed	Unsold Securities Associated with Fee Offset Claimed	Unsold Aggregate Offering Amount Associated with Fee Offset Claimed	Fee Paid with Fee Offset Source
Rules 457(b) and 0-11(a)(2)												
Fee Offset Claims	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Fee Offset Sources	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Rule 457(p)												
Fee Offset Claims	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Fee Offset Sources	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Table 3: Combined Prospectuses ☑Not Applicable

	Security Type	Security Class Title	Amount of Securities Previously Registered	Maximum Aggregate Offering Price of Securities Previously Registered	Form Type	File Number	Initial Effective Date
N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A