UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 10-K

(Mark One)

☒ **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the fiscal year ended December 31, 2022

OR

☐ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934 FOR THE TRANSITION PERIOD FROM TO**

Commission File Number 001-40800

TYRA BIOSCIENCES, INC.

(Exact name of Registrant as specified in its Charter)

Delaware	**83-1476348**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. Employer Identification No.)**
2656 State Street	
Carlsbad, California	**92008**
(Address of principal executive offices)	**(Zip Code)**

Registrant's telephone number, including area code: (619) 728-4760

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common Stock, $0.0001 par value per share	**TYRA**	**The Nasdaq Global Select Market**

Securities registered pursuant to Section 12(g) of the Act: **None**

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

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

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

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

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

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

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Indicate by check mark whether the registrant has filed a report on and attestation to its management's assessment of the effectiveness of its internal control over financial reporting under Section 404(b) of the Sarbanes-Oxley Act (15 U.S.C. 7262(b)) by the registered public accounting firm that prepared or issued its audit report. ☐

If securities are registered pursuant to Section 12(b) of the Act, indicate by check mark whether the financial statements of the registrant included in the filing reflect the correction of an error to previously issued financial statements. ☐

Indicate by check mark whether any of those error corrections are restatements that required a recovery analysis of incentive-based compensation received by any of the registrant's executive officers during the relevant recovery period pursuant to §240.10D-1(b). ☐

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

The aggregate market value of registrant's common stock held by non-affiliates of the registrant, computed by reference to the closing price as of the last business day of the registrant's most recently completed second fiscal quarter, June 30, 2022, was approximately $121.8 million.

As of March 20, 2023, the registrant had 42,436,215 shares of common stock ($0.0001 par value) outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Certain sections of the registrant's definitive proxy statement for the 2023 annual meeting of stockholders to be filed with the Securities and Exchange Commission pursuant to Regulation 14A not later than 120 days after the end of the fiscal year covered by this Form 10-K are incorporated by reference into Part III of this Form 10-K.

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PART I

FORWARD-LOOKING STATEMENTS AND MARKET DATA

This Annual Report on Form 10-K (Annual Report) contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended (the Securities Act), and Section 21E of the Securities Exchange Act of 1934, as amended (the Exchange Act). All statements other than statements of historical facts contained in this Annual Report, including statements regarding our future results of operations and financial position, business strategy, research and development plans, the anticipated timing and phase of development, costs, design and conduct of our ongoing and planned preclinical studies and clinical trials for our product candidates, the timing and likelihood of regulatory filings and approvals for our product candidates, the potential to develop product candidates and the safety and therapeutic benefits of our product candidates, our ability to commercialize our product candidates, if approved, the impact of the COVID-19 pandemic and other epidemic diseases on our business, the pricing and reimbursement of our product candidates, if approved, the timing and likelihood of success, plans and objectives of management for future operations, and future results of anticipated product development efforts, are forward-looking statements. These statements involve known and unknown risks, uncertainties and other important factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements. This Annual Report on Form 10-K also contains estimates and other statistical data made by independent parties and by us relating to market size and growth and other data about our industry. This data involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such estimates. In addition, projections, assumptions and estimates of our future performance and the future performance of the markets in which we operate are necessarily subject to a high degree of uncertainty and risk.

In some cases, you can identify forward-looking statements by terms such as “anticipate,” “believe,” “continue” “could,” “contemplate,” “estimate,” “expect,” “intend,” “may,” “plan,” “potential,” “predict,” “project,” “should,” “target,” “will” or "would" or the negative of these terms or other similar expressions. The forward-looking statements in this Annual Report are only predictions. We have based these forward-looking statements largely on our current expectations and projections about future events and financial trends that we believe may affect our business, financial condition and results of operations. These forward-looking statements speak only as of the date of this Annual Report and are subject to a number of risks, uncertainties and assumptions, including, without limitation, the risk factors described in Part I, Item 1A, “Risk Factors.” 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 management to predict all risk factors and uncertainties. Except as required by applicable law, we do not plan to publicly update or revise any forward-looking statements contained herein, whether as a result of any new information, future events, changed circumstances or otherwise. All forward-looking statements are qualified in their entirety by this cautionary statement, which is made under the safe harbor provisions of the Private Securities Litigation Reform Act of 1995.

This Annual Report includes trademarks, tradenames and service marks that are the property of other organizations. Solely for convenience, trademarks and tradenames referred to in this Annual Report appear without the ® and ™ symbols, but those references are not intended to indicate, in any way, that we will not assert, to the fullest extent under applicable law, our rights, or that the applicable owner will not assert its rights, to these trademarks and tradenames.

We maintain a website at www.tyra.bio, to which we regularly post copies of our press releases as well as additional information about us. Our filings with the Securities and Exchange Commission (SEC) are available free of charge through our website as soon as reasonably practicable after being electronically filed with or furnished to the SEC. Information contained in our website does not constitute a part of this report or our other filings with the SEC.

Item 1. Business.

Overview

We are a clinical-stage biotechnology company focused on developing next-generation precision medicines that target large opportunities in Fibroblast Growth Factor Receptor (FGFR) biology. Our in-house precision medicine platform, SNÅP, enables rapid and precise drug design through iterative molecular SNÅPshots that help predict genetic alterations most likely to cause acquired resistance to existing therapies. Our initial focus is on applying our accelerated small molecule drug discovery engine to develop therapies in targeted oncology and genetically defined conditions.

In oncology, the widespread availability of approved targeted treatments, such as kinase inhibitors, has transformed the cancer treatment landscape. Despite the therapeutic benefit that targeted oncology treatments have created for some patients, the response rate and duration of efficacy is often limited by acquired drug resistance, off-target toxicities and other shortcomings of existing therapies. We are using our proprietary SNÅP platform, which is optimized to enable rapid and precise refinement of structural design through iterative molecular SNÅPshots, in order to generate novel product candidates that are specifically designed to limit off-target toxicities and address acquired drug resistance to provide next-generation treatment options. Genomic alterations in FGFR family members occur in approximately 7% of all human cancers, representing about 126,000 new cases per year.

We are advancing multiple oncology product candidates toward the clinic, including our lead product candidate TYRA-300, an FGFR3 selective inhibitor with an initial focus on patients with metastatic urothelial carcinoma of the bladder and urinary tract (mUC). We submitted an Investigational New Drug application (IND) to the U.S. Food and Drug Administration (FDA) for TYRA-300 in June 2022 and received clearance in July 2022 to proceed with our Phase 1/2 clinical trial of TYRA-300, SURF301 (**S**tudy in **U**ntreated and **R**esistant **F**GFR3+ Advanced Solid Tumors), a multi-center, open label study designed to determine the optimal and maximum tolerated doses and the recommended Phase 2 dose of TYRA-300, as well as to evaluate the preliminary antitumor activity of TYRA-300. In November 2022, the first patient was dosed with TYRA-300 in our Phase 1/2 study SURF301.

Beyond oncology, FGFR3 is implicated in many developmental conditions, such as achondroplasia (ACH) and other skeletal dysplasias, due to its role in regulating bone and cartilage formation. In March 2023, we announced we were expanding development of TYRA-300 into achondroplasia (ACH) based on positive preclinical results demonstrated in a study performed in collaboration with the Imagine Institute in Paris, France. Achondroplasia, the most common form of dwarfism, is a skeletal dysplasia in which growth plate cartilage is affected, resulting in decreased growth of the long bones, vertebral bodies and skull base. These growth differences can result in health complications such as cranial and spinal stenosis, hydrocephalus, genu varum (bowed legs), and sleep apnea. A specific mutation in FGFR3 causes an estimated 97% of achondroplasia. We believe that the design of TYRA-300 may have a meaningful impact on achondroplasia and other skeletal dysplasias. We are planning additional IND-enabling studies and anticipate submitting an IND to the FDA to enable a Phase 2 study in pediatric achondroplasia in 2024.

We are also advancing our second oncology product candidate, TYRA-200, an FGFR1/2/3 inhibitor with potency against activating FGFR2 gene alterations, as well as clinically important molecular brake and gatekeeper resistance mutations. In December 2022, we submitted an IND to the FDA for TYRA-200 and received clearance in January 2023 to proceed with a Phase 1 clinical trial of TYRA-200, which will be focused on intrahepatic cholangiocarcinoma resistant to other FGFR inhibitors. We anticipate dosing the first patient in this trial in the second half of 2023.

Our SNÅP Platform

We developed our proprietary SNÅP platform to efficiently identify and selectively target vulnerabilities in the mutant proteins where genetic alterations have eliminated or reduced the effectiveness of targeted therapies. Through the rapid generation of precise molecular SNÅPshots, we continually gain deeper insights into the structure of inhibitor binding sites and how commonly occurring genetic alterations lead to acquired drug resistance to existing therapies. Leveraging these insights, we aim to predict the genetic alterations most likely

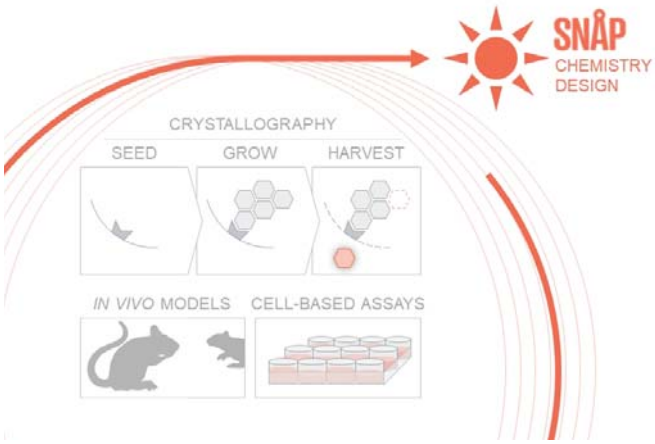
to cause resistance to specific existing therapies and develop compound candidates with innovative structures that are designed to inhibit the target while avoiding those mutations. Furthermore, we have developed this platform as a tool to fine-tune selectivity of candidates where we seek to minimize the activity of one target over another. Each SNÅPshot enables us to see protein and compound interactions on an angstrom scale, with an aim to build in selectivity for a target even among a family of proteins that share a very similar sequence identity. Through this process, we identify product candidates that may have the potency and selectivity to, if approved, be used as important treatment options to address critical unmet needs.

Our SNÅP platform is driven by our ability to generate iterative data rapidly and concurrently from the following three key pillars.

- **Protein crystallography**. We have developed proprietary protein crystallography techniques that enable us to determine the co-crystal structures of newly synthesized compounds in target proteins in as little as three days. This enables weekly generation of detailed structural insights on the precise interactions and conformational changes that occur when our potential product candidates bind to a particular target, creating opportunities to further refine the structural design.

- **Cell-based assays**. We assess inhibitor potency directly in *in vitro* target-specific anti-proliferation assays, in addition to enzymatic assays, to enable us to simultaneously understand target potency and cell penetration as well as target-specific cell killing. Our process allows us to generate data on newly synthesized compounds in as little as two days.

- ***In vivo* models**. Our direct structural insights and *in vitro* datasets are complemented by *in vivo* pharmacologic data generated through in-house animal models that provide us with bioavailability, pharmacokinetic data and anti-tumor activity in as little as five days.



SNÅP platform

Together, these three pillars of our platform provide a molecular SNÅPshot for our compound candidates. At this time, we are able to generate a molecular SNÅPshot for a compound candidate within one week. We believe that a sharp focus on efficiently generating these three key empirical datasets for compound candidates enables us to balance speed with the robust identification of pivotal insights to rapidly and precisely iterate the design of our novel molecular structures.

Our Programs

Below is an overview of our programs.

Our FGFR3 Program—TYRA-300

In oncology, we are developing our lead product candidate, TYRA-300, a selective inhibitor of FGFR3, for the treatment of patients with mUC and other solid tumors with activating mutations in FGFR3. One common mechanism of acquired drug resistance in kinases such as FGFR3 is the emergence of gatekeeper mutations. For example, the V555M and V555L gatekeeper mutations have been shown to block access to a portion of the binding pocket accessed by first generation pan-FGFR inhibitors, such as Balversa (erdafitinib), the only currently FDA approved FGFR-targeted therapy for mUC, as well as Pemazyre (pemigatinib), Truseltiq (infigratinib), and Lytgobi (futibatinib), which are pan-FGFR inhibitors approved for intrahepatic cholangiocarcinoma. Because we believe the gatekeeper mutation represents a key limitation to the efficacy and durability of first generation FGFR inhibitors, we have designed TYRA-300 to avoid interactions with the gatekeeper region of the FGFR binding site. In cell-based assays and preclinical xenograft models, we observed that TYRA-300 had similar potency against cells harboring the wild-type or the gatekeeper mutations.

In addition to addressing the gatekeeper resistance mutations, we have designed TYRA-300 to be more selective for FGFR3 over FGFR1, FGFR2, and FGFR4 to minimize off-target side effects, providing potential clinical advantages over less selective first-generation compounds. The product labels of first generation inhibitors report high discontinuation and dose reduction rates, ranging from 23% for pemigatinib to 75% for infigratinib. Each approved inhibitor reports hyperphosphatemia (60%+), which is a well-characterized adverse event, due to FGFR1 inhibition. Hyperphosphatemia is an electrolyte disorder characterized by an elevated level of phosphate in the blood. Hyperphosphatemia is commonly observed in patients treated with these inhibitors, and is the dose-limiting toxicity for erdafitinib, which may potentially limit its efficacy. This is particularly important in the mUC population, where more than half of patients are ineligible for cisplatin therapy due to underlying renal dysfunction, making hyperphosphatemia resulting from pan-FGFR inhibitors more difficult to manage. FGFR2 drives potentially debilitating oral, nail, ocular, and skin toxicities, and FGFR4 drives toxicities related to bile acid synthesis such as diarrhea and increases in liver enzyme, AST (aspartate aminotransferase) and ALT (alanine transaminase) levels.

In addition, we believe that if we are able to establish a differentiated tolerability profile for TYRA-300, we will have the potential to pursue additional indications, including a large population of patients with non-muscle invasive bladder cancer (NMIBC) as well as other FGFR3-driven conditions, where pan-FGFR inhibitors may see limited use due to toxicity from inhibition of FGFR1, FGFR2, and FGFR4. It is estimated that a majority of the approximately 80,000 annual cases of urothelial cancer in the United States are initially diagnosed as NMIBC, where up to 80% may harbor FGFR3 activating mutations. This represents a potential outsized opportunity in oncology relative to most other targeted therapies. The risk of recurrence of NMIBC, or progression to muscle-invasive disease (MIBC), results in long term urologic follow up and treatment, which may ultimately lead to

surgical removal of the bladder (cystectomy). Interim data presented in a poster at the American Society for Clinical Oncology (ASCO) Genitourinary Cancer Symposium in February 2023 for erdafitinib in intermediate risk NMIBC and BCG-unresponsive high-risk NMIBC generally showed high complete response rates. The safety results reported were generally consistent with that known for erdafitinib, despite using a lower (6 mg) daily dose. A well-tolerated oral drug that can address this population could provide an important bladder-sparing alternative in this large patient population.

Our FGFR3 Achondroplasia and Skeletal Dysplasia Program

Beyond oncology, mutations in FGFR3 are implicated in a family of skeletal conditions due to its role in regulating bone and cartilage formation. We believe that there is an opportunity to develop TYRA-300 to potentially address the long-term complications associated with these rare skeletal conditions including achondroplasia, hypochondroplasia, thanatophoric dysplasia, and other FGFR3-driven genetic syndromes. Our structural insights into FGFR3-selective chemistry from TYRA-300 may provide an opportunity to develop an oral therapy that provides significant benefit to these children.

In March 2023, we announced we were expanding development of TYRA-300 into achondroplasia based on positive preclinical results demonstrated in a study performed in collaboration with the Imagine Institute in Paris, France. In the study, TYRA-300 was evaluated in FGFR3 wild-type and mutant preclinical models to measure increases in growth and bone length, compared to vehicle-treated mice. In an FGFR3$^{Y367C/+}$ model, TYRA-300 was administered daily at a 1.2 mg/kg dose for 15 days. TYRA-300 increased body length in mice by 17.6% compared to the vehicle ($p<0.0001$) and increased the length of the femur (+24.4%), tibia (+38.3%) and L4-L6 (+23.9%) in mice ($p<0.0001$). We are planning additional IND-enabling studies and anticipate submitting an IND to the FDA to enable a Phase 2 study in pediatric achondroplasia in 2024.

Our FGFR2 Program

Our second product candidate, TYRA-200, is an FGFR1/2/3 inhibitor with potency against activating FGFR2 gene alterations, as well as clinically important molecular brake and gatekeeper resistance mutations. We will study TYRA-200 initially in FGFR2-driven Intrahepatic cholangiocarcinoma (ICC) resistant to previous FGFR inhibitors. Acquired resistance mutations, such as gatekeeper and molecular brake mutations, have been observed in patients treated with Pemazyre (pemigatinib), Truseltiq (infigratinib), and Lytgobi (futibatinib), three FDA approved FGFR inhibitors for ICC. Newer agents in the clinic, such as RLY-4008 and TT-00420, thus far have shown limited activity against some of these key resistance mutations in the clinic, indicating that acquired resistance remains an area of high unmet need. We have designed TYRA-200 to be active against nearly all of the clinically identified acquired resistant mutations that arise during treatment with other FGFR inhibitors, which we believe is necessary to address the problem of disease progression due to polyclonal resistance. In December 2022, we submitted an IND to the FDA for TYRA-200 and received clearance in January 2023 to proceed with a Phase 1 clinical trial of TYRA-200. We anticipate dosing the first patient in this trial in the second half of 2023.

Our FGFR4/FGF19 and RET Programs

We are also progressing next generation pipeline candidates designed to address FGFR4/FGF19 and RET-related cancers. Our FGFR4/FGF19 program is initially focused on hepatocellular carcinoma (HCC), where FGF19 overexpression has been shown to be an important driver in a subpopulation of HCC. Recent insights into FGF/FGFR signaling in HCC indicates the potential for our candidate molecule to address an important bypass mechanism as well as acquired resistance mutations that have limited the efficacy of previous FGFR4-specific inhibitors. In addition, we are exploring a novel mitigation strategy that may address dose-limiting FGFR4-specific toxicity seen with previous inhibitors.

Our RET program is focused on overcoming acquired drug resistance mutations that are clinically observed to arise in response to treatment with Retevmo (selpercatinib), Gavreto (pralsetanib), Cometriq (cabozantinib), and/or Caprelsa (vandetanib). In addition, our RET candidate's profile potentially will be further differentiated based on increased brain exposure to address brain metastases, which remains an important unmet need of current therapies.

Our Strategy

At Tyra, we do not accept that cancer patients with acquired drug resistance should be left with the devastating reality of limited or no treatment options or that people with genetically defined conditions should not have treatment options providing meaningful medical benefit. Our vision is to become a leading biotechnology company utilizing our unique approach to designing and developing next-generation precision medicines that target large opportunities in FGFR biology. Key elements of our strategy to achieve our vision are as follows:

- **Advance next generation precision medicines through clinical development and regulatory approval.** We are developing our oncology product candidates with a goal of overcoming acquired resistance and off-target toxicities that result in reduction of the therapeutic effects of less selective pan-FGFR inhibitors. We are initially developing TYRA-300 for patients with mUC, where a more selective, gate keeper agnostic, inhibitor may be more potent, better tolerated, and result in higher response rates and longer duration of responses. While TYRA-300 is being evaluated initially in mUC, we believe that a better tolerated, highly selective molecule can address earlier NMIBC disease, where a balance of efficacy and tolerability are important factors for patient adherence and acceptance. We submitted an IND to the FDA for TYRA-300 in June 2022 and received clearance in July 2022 to proceed with our Phase 1/2 clinical trial of TYRA-300, SURF301 (**S**tudy in **U**ntreated and **R**esistant **F**GFR3+ Advanced Solid Tumors), an international multi-center, open label study designed to determine the optimal and maximum tolerated doses and the recommended Phase 2 dose of TYRA-300, as well as to evaluate the preliminary antitumor activity of TYRA-300. In November 2022, the first patient was dosed with TYRA-300 in SURF301.

  In March 2023, we announced we were expanding development of TYRA-300 into achondroplasia (ACH) based on positive preclinical results demonstrated in a study performed in collaboration with the Imagine Institute in Paris, France. We are planning additional IND-enabling studies and anticipate submitting an IND to the FDA to enable a Phase 2 study in pediatric achondroplasia in 2024.

  Our second product candidate, TYRA-200, is an FGFR1/2/3 inhibitor that is specifically designed to retain potency against all of the known resistance mutations that arise in ICC patients who are treated with other FGFR inhibitors. No other FGFR inhibitors retain potency across all of these mutations to the same degree as TYRA-200 in vitro. We hypothesize that each FGFR inhibitor will select for resistance mutations for which they have the least potency, resulting in disease progression and treatment failure. We believe the ability to address the breadth of mutations with TYRA-200 fills an important unmet need in this population of ICC patients and could drive longer duration of response compared to other FGFR inhibitors. In December 2022, we submitted an IND to the FDA for TYRA-200 and received clearance in January 2023 to proceed with our Phase 1 clinical trial. This study will initially focus on demonstrating whether TYRA-200 can provide clinical benefit to patients who had an initial response and then progressed on a prior FGFR inhibitor due to acquired resistance mutations. We expect to dose the first patient in this study in the second half of 2023.

- **Harness the strength of our SNÅP platform to rapidly develop additional next-generation precision therapies**. We believe our SNÅP platform has disrupted the conventional process used to discover differentiated product candidates, resulting in what we believe is a significantly condensed time frame. Leveraging our SNÅP platform, we have rapidly developed an expanding pipeline of product candidates since our founding in August 2018. Although our initial focus has been on a specific set of drug targets, our SNÅP platform can be extended to multiple gene families and therapeutic areas. We plan to leverage our SNÅP platform to expand our pipeline with additional oncology and non-oncology indications where there is high unmet need.

- **Leverage the recent advances in the precision medicine landscape to potentially expedite our product candidates' development.** There have been multiple recent accelerated approvals by the FDA of targeted therapies based on compelling clinical outcomes from single-arm dose expansion cohort clinical trials. Recent accelerated approvals have been conditionally granted in as little as

three years from initial clinical testing. Our clinical programs are designed to address important unmet medical needs, which may allow us to leverage these precedents used by recently approved precision oncology and rare disease drugs to seek expedited regulatory review(s) and approval(s) if we successfully develop one or more of our product candidates. However, we have not discussed accelerated approval with the FDA for any of our programs, and as a result, there is no assurance that an accelerated pathway will be available to us or that it will lead to a faster development process or a faster regulatory review. While an accelerated pathway may potentially expedite development or the approval process, it does not change the FDA's standards of approval or increase the likelihood that a product candidate will receive approval.

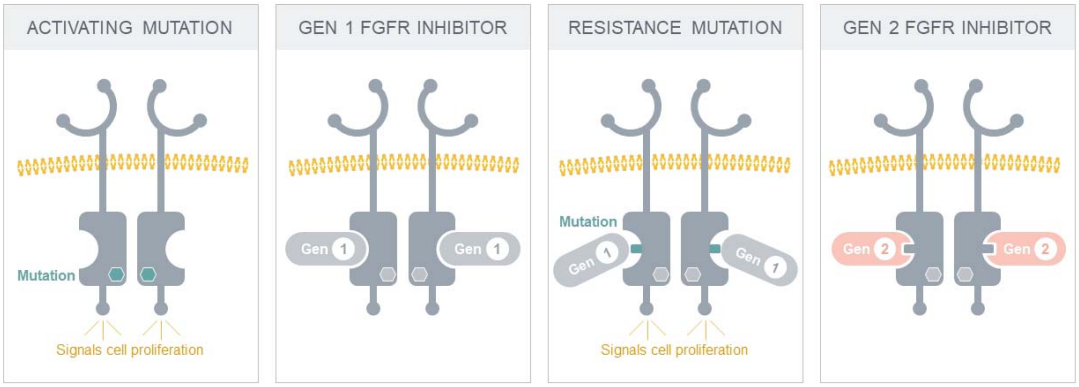
In addition, advances in next-generation genomic sequencing, particularly blood-based assays (liquid biopsy), continue to expand access to information that helps patients and their physicians identify potential personalized therapies that address tumor and germline mutations. We believe increasing access to liquid biopsy in our clinical trials may assist us in identifying and enrolling patients, thereby allowing us to accelerate the development timeline of our product candidates.

- **Maximize the value of our product candidates across multiple therapeutic areas through accelerated development and potential partnerships**. We believe that our ability to generate product candidates with improved selectivity for the target of interest enables the possibility of designing and developing product candidates for indications outside of oncology. Specifically, we believe we can apply our SNÅP platform to targets, such as FGFR3, that have data validating their role in the pathogenesis of genetic conditions, including achondroplasia and other skeletal dysplasias. We currently retain worldwide rights to all of our product candidates. We will consider entering into compound, target or geographic specific strategic partnerships on an opportunistic basis if we believe that such a partnership can accelerate the development and/or maximize the market potential of a product candidate.

Background

Protein kinase inhibitors in cancer and the challenge posed by acquired drug resistance

Receptor tyrosine kinases (RTKs) are a family of proteins that respond to external growth factors affecting cell proliferation. In cancer, RTKs can be constitutively activated though gain-of-function mutations or gene rearrangements, driving tumor growth. Protein kinase inhibitors are a class of targeted therapies that can effectively block protein kinase signaling and cause tumor regression. These targeted therapies have delivered profound therapeutic benefits in the treatment of cancer. As of March 1, 2023, there were over 50 FDA-approved protein kinase inhibitors for the treatment of cancer, targeting about two dozen different protein kinases. Despite the success of these drugs, they have been susceptible to acquired drug resistance and reduction of effect, leaving patients with limited or no treatment options. In particular, these current or first-generation kinase inhibitors lose potency in response to mutations that prevent the drug from binding to the target protein, allowing the kinase to continue to function resulting in continued tumor growth. This mutation, and resulting loss of potency from these kinase inhibitors, results in the patient's cancer becoming refractory to treatment and the patient regressing.



Overview of RTK activating mutations and acquired drug resistance mutations

Development of acquired drug resistance to kinase inhibitors is common among protein kinases. Acquired on-target resistance has emerged in nearly every validated target, including FGFR, RET, epidermal growth factor receptor (EGFR), anaplastic lymphoma kinase (ALK), KIT, neurotrophic tropomyosin receptor kinase (NTRK), ROS1 and mesenchymal epithelial transition factor (MET). These key resistance mutations can be generally grouped into four classes:

- **Gatekeeper.** Mutations such as BCR-ABL T315I and EGFR T790M are known as gatekeeper mutations because they are found at a key location at the entrance to a hydrophobic pocket in the back of the adenosine triphosphate (ATP) binding site that many kinase inhibitors access to increase potency and obtain specificity.

- **Molecular brake.** Activating mutations in the kinase domain of RTKs are associated with the development of many forms of cancer. A number of these mutations cluster in a hinge region of the kinase structure, resulting in kinase activation by disengaging a highly conserved region referred to as a molecular brake.

- **Cys mutant.** Irreversible kinase inhibitors, such as Tagrisso (osimertinib), typically covalently attach to cysteine residues in the kinase active site. EGFR C797S and corresponding mutations in cysteine residues of other kinases prevent binding and block the activity of these inhibitors.

- **Solvent front.** Certain kinase inhibitors obtain their specificity by interacting with amino acid residues located at the opening of the ATP binding site to solvent. Mutations in these residues that lead to drug resistance are referred to as solvent front mutations.

The rapid rise of mutations that enable tumors to become resistant to previous generations of kinase inhibitors poses a challenge to drug developers, one that we believe will demand innovation for a long time to come.

Commercial success of next-generation kinase inhibitors

Osimertinib is an example of how a next-generation kinase inhibitor can not only overcome the limitations of acquired drug resistance to first generation therapies, but also demonstrate broader applicability across different lines of therapies. While first generation EGFR inhibitors, such as Iressa (gefitinib) and Tarceva (erlotinib), led to significant improvements in tolerability compared to standard of care chemotherapy, on average, tumor responses last only six to twelve months before disease progression. About 50% of treated patients developed drug resistance due to a gatekeeper mutation at T790M. Osimertinib's ability to overcome this key gatekeeper mutation, which limited the duration of efficacy of first generation EGFR inhibitors, has contributed to osimertinib realizing 2022 sales of $5.4 billion, more than double the amount of the peak sales achieved by the two first generation inhibitors in 2013. In addition to its ability to overcome the gatekeeper mutation, osimertinib also displayed higher

mutant selectivity and other performance enhancements resulting in greater tolerability, safety and efficacy. When used earlier in treatment, osimertinib nearly doubled progression-free survival compared to gefitinib or erlotinib with a better overall safety profile.

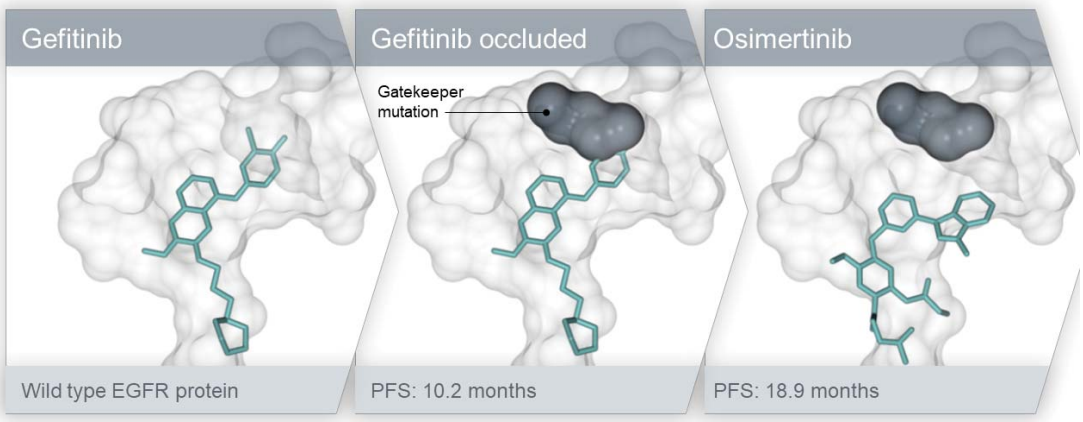
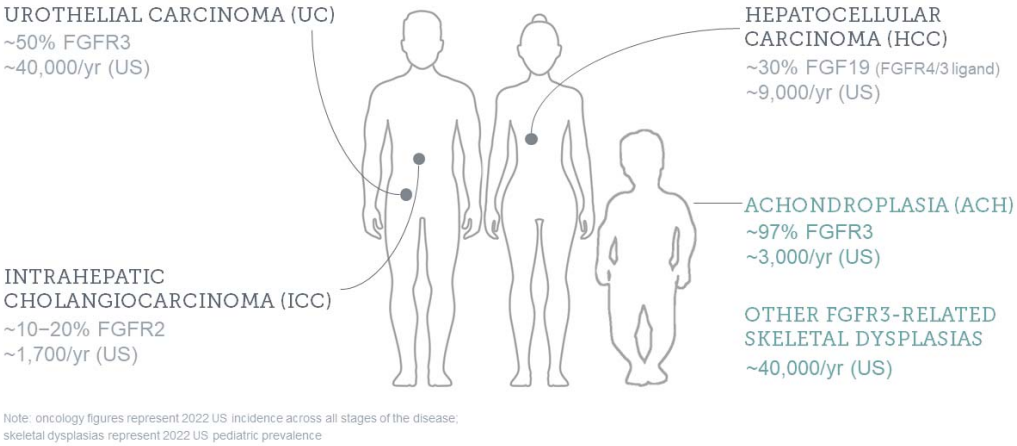


Illustration of osimertinib overcoming gatekeeper mutations

FGFR gene alterations in cancer and skeletal dysplasias

The FGFR family consists of four highly conserved RTKs, FGFR1-4. These receptors regulate a variety of cellular functions, including proliferation, differentiation, and survival. Genomic alterations in FGFR family members occur in approximately 7% of all human cancers, representing about 126,000 new cases a year. These genomic alterations, many of which lead to increased FGFR activity, have been found in cancers throughout the body, as shown in the figure below. The highest FGFR alteration frequencies are seen in urothelial cancer, ICC, hepatocellular carcinoma, endometrial cancer, lung cancers, breast cancer and cervical cancer. FGFR3's critical role in chondrogenesis presents multiple sizeable opportunities outside of oncology. Alterations in FGFR3 have been found to drive greater than 97% of Achondroplasia cases and additional FGFR3-related skeletal dysplasias, with a total addressable prevalence exceeding 40,000 children per year.



Alterations in FGFR drive many cancers and skeletal dysplasias

Four FGFR targeted therapies have been approved by the FDA for oncology: erdafitinib for locally advanced or metastatic urothelial carcinoma, or bladder cancer, and pemigatinib, infigratinib, and futibatinib for ICC with FGFR2-fusions or gene rearrangements. These inhibitors have demonstrated clinical responses, however

response rates and duration of response are limited. While patients may initially respond to FGFR targeted therapies, many develop acquired drug resistance, ultimately resulting in disease progression and discontinuation of therapy. Decreased activity of erdafitinib and pemigatinib due to resistance mutations that alter their ability to bind to the active site, such as gatekeeper mutations, has been observed. Gatekeeper mutations have also been seen in patients in a clinical trial treated with infigratinib while acquired-resistance molecular brake mutations have been seen in patients in clinical trials of pemigatinib, infigratinib and futibatinib. Off-target toxicities driven by FGFR1, 2, and 4 selectivity have also driven high rates of dose reductions and discontinuations, limiting treatment duration and potential efficacy for patients.

Beyond oncology, the FGFR3 pathway has been clinically validated in achondroplasia. In 2021, BioMarin Pharmaceutical's Voxzogo, a once daily injectable C-naturetic peptide (CNP) analog was granted accelerated approval in the United States for children with achondroplasia who are 5 years of age and older. CNP acts as a positive regulator of the signaling pathway downstream of FGFR3 to promote endochondral bone growth. Voxzogo approval was based on a 1.57cm/year mean annual height velocity improvement versus placebo. While the approval of Voxzogo is an important milestone in the treatment of children with achondroplasia, the long-term therapeutic benefit of increasing growth velocity is not yet known and the daily injection regimen for Voxzogo is also challenging for children and their parents. BridgeBio Pharma, Inc. (BridgeBio) is developing low dose infigratinib, an oral FGFR 1/2/3 inhibitor for achondroplasia, and in 2023 announced preliminary data for 10 of 12 subjects (Cohort 5, 0.25 mg/kg once daily) demonstrating a mean annual height velocity improvement of 3.03cm/year over baseline growth velocity. We believe TYRA-300, a once-daily oral FGFR3 selective inhibitor, may have a meaningful impact for children with achondroplasia and other skeletal dysplasias.

Our Approach and Solution

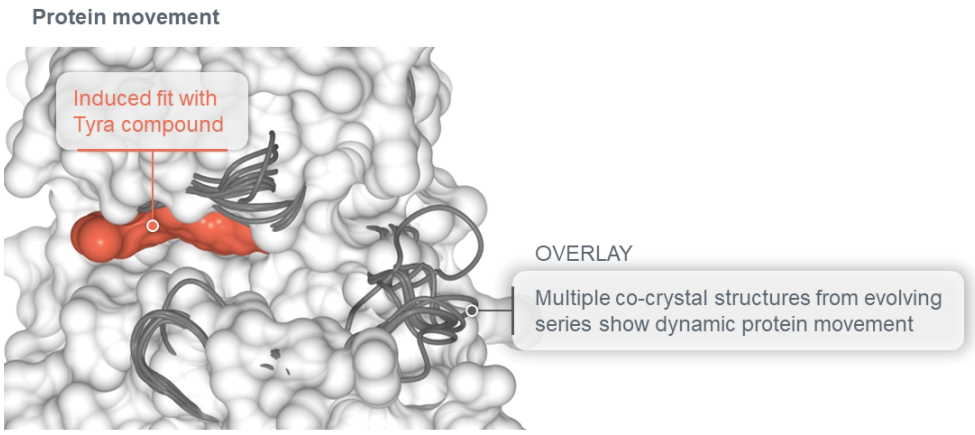
Our SNÅP platform

We developed our proprietary SNÅP platform to efficiently identify and selectively target vulnerabilities in the mutant proteins where genetic alterations have eliminated or reduced the effectiveness of current targeted therapies. Our SNÅP platform is driven by our ability to generate iterative data rapidly and concurrently from three key pillars. Rapid generation of crystallographic data, use of custom cell-based assays and *in vivo* models comprise the three pillars of our platform. We leverage our platform to identify and develop product candidates that may have the potency and selectivity to address the liabilities that acquired drug resistance has created for other therapies. Collectively, our efforts to optimize and integrate these three pillars in parallel have enabled us to condense our design cycles and more quickly develop high quality, differentiated product candidates.

Rapid generation of crystallographic data

We have streamlined the use of protein crystallography to visualize the interaction of our potential product candidates with binding pockets of protein kinases. Through our proprietary methods, we can rapidly induce crystal formation and enhance crystal durability. Together, this reduces the time required to generate new crystal structures. We routinely generate co-crystal structures on newly synthesized compounds in as little as three days, a pace that allows us to continually refresh and, we believe, improve our insights into the features and structures that enable us to discover compounds that are potent and selective inhibitors of our targets. The rapid and iterative nature of our proprietary approach also allows us to address known mutations and potentially avoid future mutations.

While conventional discovery approaches prioritize computational simulations based on a small number of structures or structural models, we believe the ability to generate a large amount of empirical data obtained from many protein crystal structures is more informative and allows us to better design our product candidates. We are able to sustain rapid crystallography throughput, enabling the generation of graphical images of protein structures with and without bound inhibitors that, when combined with enzyme, cell and *in vivo* assays, comprise molecular SNÅPshots. These structures show the exact binding conformation of small molecules to our protein targets as well as the variations in protein structure that they induce at a resolution down to a single tenth of an angstrom (Å). We iterate rapidly between the wet lab and the crystallography lab and believe that the resulting datasets provide us with robust empirical data more quickly relative to conventional approaches as we seek innovative compounds that can potentially improve the selectivity and acquired drug resistance activity seen with other kinase inhibitors.



We capture variations in ligand-protein interactions by generating molecular SNÅPshots of many ligands

This figure shows several structures of the same protein which has been co-crystallized with different inhibitors. Certain regions of the protein, shown as dark gray loops, assume different conformations in the presence of different ligands. The plasticity of the protein revealed by these structures informs our drug design.

Custom cell-based assays

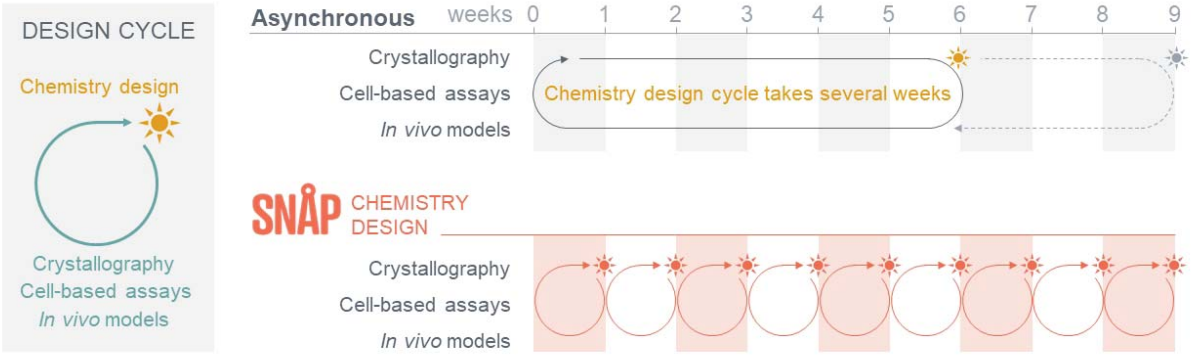
Determining the potency, selectively and cytotoxicity of our compounds early through custom cell-based assays allows us to rapidly evaluate, design and optimize our potential product candidates. The cell-based assays we use are a combination of cell lines derived from naturally occurring tumors and treatment-resistant tumors as well as engineered cell lines in which specific kinases or kinase mutations are introduced to create panels of isogenic cells. By providing direct evidence of cell penetration and target engagement, we believe these assays yield more meaningful information about the potential of our compounds compared to the artificial system of purified proteins used in standard enzymological screens. While we also assess the potency and selectivity of our compounds using enzyme assays, these assays primarily serve to provide concordance to the validity of our cell-based assays. As a result, these cellular systems are our primary screening tools to progress our potential product candidates. We are able to run newly synthesized compounds through these cell-based assays in as little as two days, helping to drive a rapid, iterative drug design cycle.

In vivo models

The ability to rapidly assess the potential of our compounds through *in vivo* models to determine their pharmacokinetic/pharmacodynamic parameters in addition to their target-specific antitumor activity is paramount. We establish and validate the majority of our models in-house, which allows us to rapidly test new compounds and to collect actionable data in as little as five days. We feed this information back into our design cycle, allowing us to condense the traditional drug discovery timeline, prior to commencing clinical development.

A tight compound design, synthesis and testing loop

Our philosophy is to execute activities such as obtaining crystal structures, assaying for cellular activity and generating *in vivo* data not as a set of sequential steps, but rather in concurrence in order to save time. Whereas more traditional drug discovery efforts may rely upon the availability of crystallographic and *in vivo* model data at monthly intervals, we strive to generate this data on a weekly basis. We do not wait to determine if a compound passes a potency test in a cell-based assay before evaluating it in other assays, with the explicit understanding that there is key knowledge to be gained from compounds that are not as potent as expected.



Our synchronized and compressed data generation cycle time allows us to accelerate drug discovery by allowing the execution of more drug design cycles in a fixed amount of time

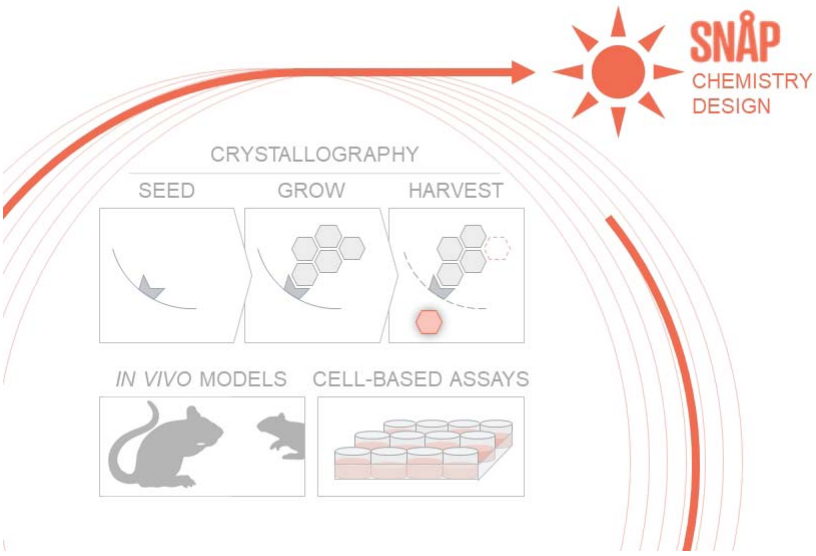
Our ever-growing understanding of protein and inhibitor interactions, deepened by the crystal structures we continue to generate, provides insights that we leverage in product candidate engineering. We combine these potency and selectivity predictions with metabolic stability, bioavailability and pharmacokinetics data to design small molecules with the chemical properties required to become potential product candidates. In a single weekly drug discovery cycle, we profile newly synthesized compounds as follows.

(1) Generating a crystal structure with a target protein in as little as three days.

(2) Evaluating activity in ‘on-target’ and ‘off-target’ cell-based assays in as little as two days.

(3) Measuring, efficacy, or tumor growth inhibition (TGI), of newly synthesized compounds in as little as five days.

Taken together, the high-resolution structural data and preclinical experiments inform new chemistry designs that are rapidly synthesized for evaluation in our next weekly drug discovery cycle. This process, enabled by trade-secrets and proprietary engineered assays, comprises our SNÅP platform. Our highly experienced team of medicinal chemists efficiently utilizes our platform to rapidly synthesize compounds designed to further optimize potency and selectivity, among other properties, while avoiding interactions with mutations which are known to induce drug resistance to other kinase inhibitors.



SNÅP platform

Targeted Oncology

Targeted oncology therapies approved by the FDA since 2018 have received their initial approvals in as little as three years after their first-in-human dosing began. FDA guidance indicates that the agency may accept overall response rate data from single-arm clinical trials as evidence of substantial clinical benefit that is sufficient for accelerated approval in settings with an unmet medical need. The nature of our clinical programs address areas of high unmet medical need, and based on these precedents, we believe that our product candidates may be eligible for accelerated approval should they demonstrate appropriate safety and efficacy in our clinical trials. However, we have not yet discussed criteria for accelerated approval with the FDA for any of our programs, and as a result, there can be no assurance that an accelerated pathway will be available for us or that it will lead to a faster development process or a faster regulatory review. While an accelerated pathway may potentially expedite development or the approval process, it does not change the FDA's standards of approval or increase the likelihood that a product candidate will receive approval. In fact, recent guidance from FDA has indicated greater scrutiny of the accelerated approval process, particularly with regard to enrollment and readout of confirmatory trials needed for full approval.

Our FGFR3 Program—TYRA-300 for Oncology

We are developing TYRA-300, a selective inhibitor of FGFR3, for the treatment of patients with mUC and other solid tumors with activating mutations in FGFR3. Resistance to approved and investigational pan-FGFR inhibitors has been shown to arise due to mutations in the gatekeeper region of FGFR3. We have designed TYRA-300 to avoid this region of FGFR3 and, in preclinical models to date, TYRA-300 has demonstrated similar potency against both wild-type and resistant FGFR3 targets. In addition, we have designed TYRA-300 to be more selective for FGFR3 over FGFR1, FGFR2, and FGFR4, to minimize side effects resulting from inhibition of these related proteins and achieve greater potency against the FGFR3 driver mutation. We believe this differentiation will enable us to expand into multiple cohorts of FGFR3-driven cancer including mUC patients naïve to prior FGFR therapy, tumor agnostic populations, as well as patients with intermediate- and high-risk NMIBC. Although no head-to-head clinical trials have been conducted, we believe the use of comparative in vitro and in vivo data from pre-clinical studies provides meaningful insight into the potential for our product candidates to improve on certain characteristics of approved and investigational FGFR inhibitors and helps inform potential future clinical development of our product candidates.

Market Opportunity

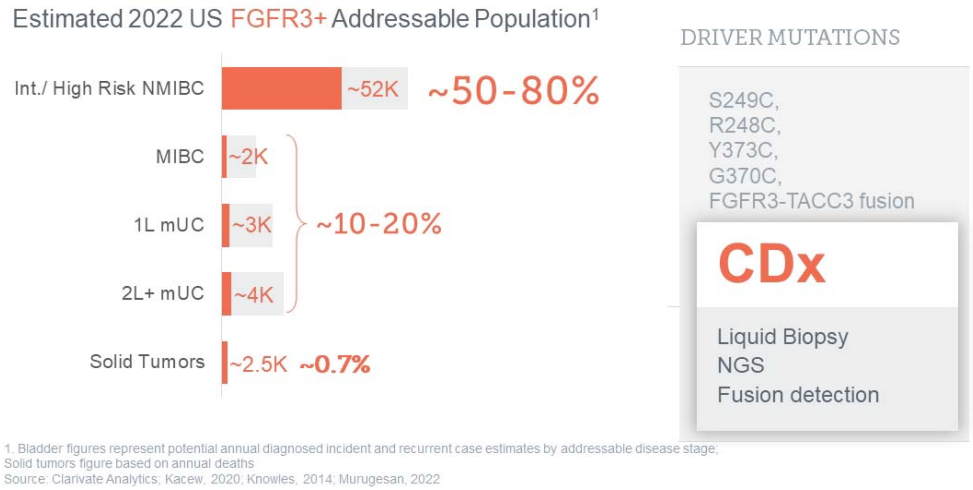
Urothelial cancer disease background

Urothelial cancer (UC) is one of the most common malignancies of the genitourinary system and can involve the bladder or the upper urinary tract. Patients with UC classically present with painless blood in the urine. However, because this symptom is similar to those of benign disorders, such as urinary tract infections, cystitis, prostatitis and the passage of kidney stones, diagnosis of UC is often delayed as these other, more common, conditions are ruled out. Delays in diagnosis can lead to worse outcomes due to the presence of more advanced stage disease by the time a diagnosis of UC is made. We refer to bladder cancer, NMIBC and muscle invasive bladder cancer (MIBC) when describing localized disease, and UC and mUC when describing a population that includes both bladder and upper urinary tract cancers.

An estimated 81,180 new cases of bladder cancer and 17,100 deaths are projected for 2022 in the United States and over 700,000 people were living with bladder cancer in the United States in 2019. Globally, bladder cancer accounted for approximately 550,000 new cases and 200,000 deaths in 2018. Bladder cancer itself is classified into two broad categories: NMIBC where the cancer is restricted to surface lining of the bladder; and MIBC, which is a cancer that has grown deeper into the bladder wall and has a higher potential metastatic spread. Approximately 30% of newly diagnosed cases of bladder cancer are MIBC. Of the remaining 70% of new diagnoses of bladder cancer that are NMIBC cases, an estimated 10 to 15% progress to MIBC. Whereas the five-year survival for early stage NMIBC is 96%, it falls to 6.4% for metastatic MIBC.

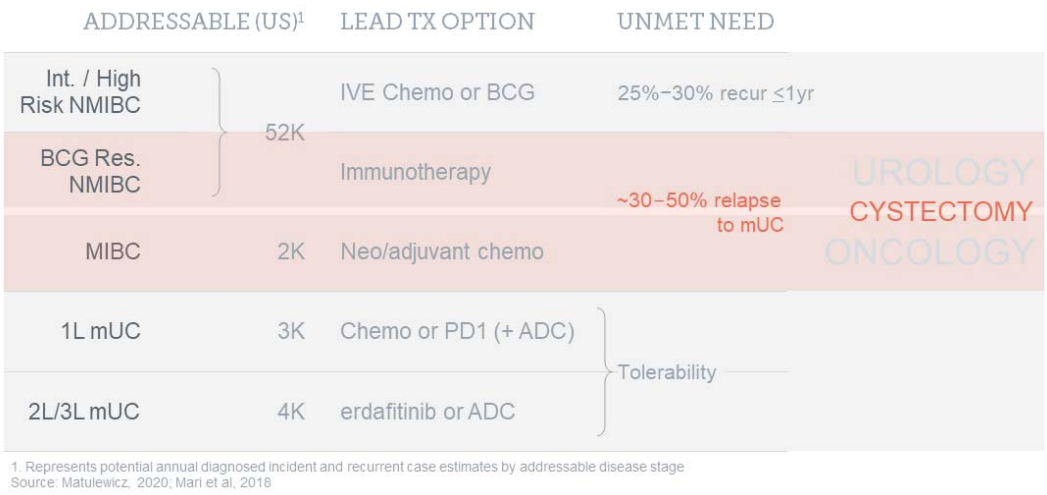
FGFR3 is a protein receptor expressed on the cell surface that stimulates cellular proliferation upon binding of a fibroblast growth factor. Uncontrolled activation of FGFR3 has been implicated in the oncogenesis of multiple solid tumor types. The incidence of activating FGFR3 mutations in bladder cancer has been estimated to be as high as 80% in NMIBCs and up to 20% of mUC, making FGFR3 an attractive target for development.

Clarivate Analytics estimates that in 2022, across NIMBC, MIBC and mUC, approximately 160,000 patients were seeking therapy for first-time treatment or to address a recurrence. Applying FGFR3 alteration incidence to Clarivate Analytics' estimates, we believe that approximately 60,000 FGFR3+ patients are addressable across intermediate and high risk NMIBC, MIBC and mUC in the United States alone. Additionally, studies indicate that approximately 0.7% of solid tumors outside of bladder cancer are driven by FGFR3 alterations.



Potential patient populations for our FGFR3 inhibitor

Limitations of current therapies



There are high unmet needs in all stages of bladder cancer

Standard of care and current limitations for the treatment of locally advanced or metastatic UC

Patients suffering from locally advanced or metastatic UC have limited treatment options and there continues to be a high unmet need. These options come with significant toxicities, lack of durable response, and potential diminished quality of life. The initial standard treatment for patients is typically platinum-based chemotherapy with cisplatin (or carboplatin) in combination with gemcitabine. Unfortunately, the median overall survival for patients treated with chemotherapy is only 12.7 months. Following chemotherapy, patients may receive immunotherapies, such as Bavencio (avelumab) as maintenance therapy or Keytruda (pembrolizumab) after progression on chemotherapy. Responses to immunotherapy are limited and overall survival for immunotherapy is 10.3 months on average. Alternatively, patients may also receive other chemotherapies, such as Taxotere (docetaxel), Taxol (paclitaxel), or Javlor (vinflunine) alone, however overall survival is typically no greater than 7 to 9 months in select patients. A recent Phase 3 study demonstrated that the antibody-drug conjugate Padcev (enfortumab vendotin) improved overall survival to 12.8 months compared to chemotherapy following disease progression after initial platinum-containing chemotherapy and immunotherapy. Further, a combination of Padcev and Keytruda demonstrated an overall response rate of 65% in a randomized study treating 1L patients who were ineligible to receive cisplatin due to renal insufficiency or other comorbidity. The results from this study were submitted to the FDA for consideration of an accelerated approval, with a PDUFA date of April 21, 2023. A randomized Phase 3 study of Padcev + Keytruda vs combination platinum-containing chemotherapy (gemcitabine + cisplatin or carboplatin) is expected to report results in late 2023. These results are greatly anticipated, as the Padcev + Keytruda combination may become the new standard of care in 1L mUC, which in turn will possibly change the landscape of subsequent lines of therapy. Additional novel therapies include Trodelvy (sacituzumab govitecan-hziy), another antibody-drug conjugate targeting the Trop-2 receptor, which was recently granted accelerated approval for mUC following treatment with platinum-containing chemotherapy and a checkpoint inhibitor based upon an overall response rate of 33.3%. It should be noted that despite these recent advances, modest increases in overall response rates and overall survival come at a cost of significant toxicities resulting in frequent dose reductions and discontinuations, and we believe highlights the unmet need for therapies with greater efficacy and tolerability.

Standard of care and current limitations for the treatment of localized MIBC

Patients suffering from localized MIBC are potentially curable with surgery, which may include trans-urethral resection (TURBT) partial cystectomy (partial removal of the bladder), or radical cystectomy (complete removal of the bladder and nearby lymph nodes) depending on the stage of the tumor. For those who are not physically able or willing to undergo surgery, localized radiation to the bladder is an option, but local recurrence

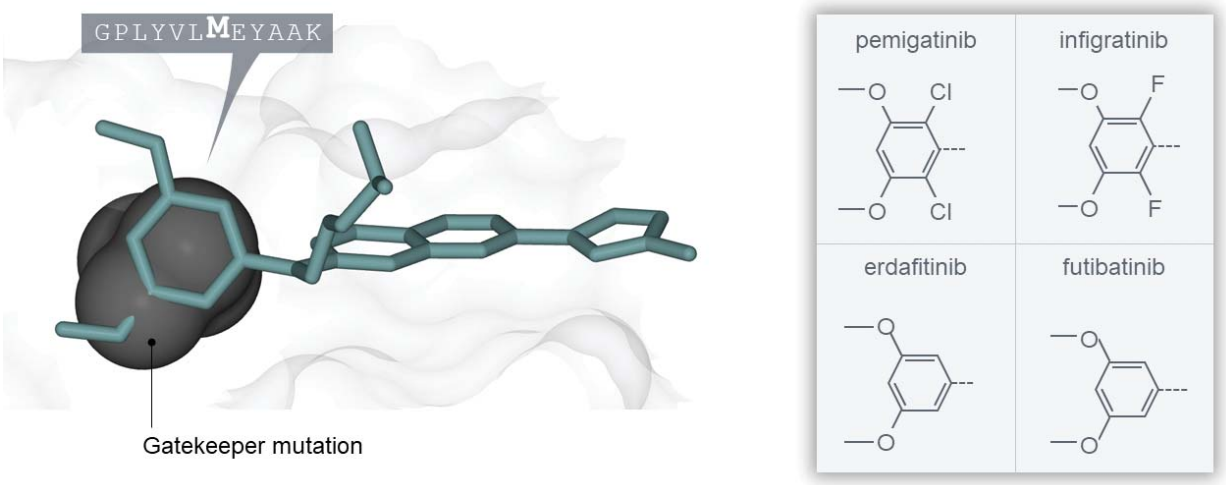
rates are high, survival rates are no better than surgery, and few contemporary randomized studies have been performed comparing radiation and surgery in the same population of patients. TURBT and partial cystectomy are reserved for highly selected patients with earlier stage tumors, often combined with neoadjuvant chemoradiotherapy for those who are willing and able to tolerate such aggressive therapy. Despite these strict criteria, recurrence rates are high (as high as 60% in some series). For the majority of patients who can have surgery, complete removal of the bladder and lymph nodes remains the only potentially curative treatment option. However, despite such a life altering operation, recurrence of metastatic disease is estimated to be 50%, highlighting the need for effective adjuvant therapies that can decrease the risk of recurrence. Nivolumab was recently approved for the adjuvant treatment of patients at high risk for recurrence following surgery for bladder cancer. While there are currently no approved targeted therapies available for MIBC, a number of tyrosine kinase inhibitors are being studied in this setting. We believe that effective oral therapies that can reduce the rate of recurrence following surgery remains a high unmet need.

Standard of care and current limitations for the treatment of NMIBC

NMIBC comprises the largest population of bladder cancer patients, representing 70-75% of cases diagnosed annually in the United States. Initial evaluation consists of local resection to confirm the diagnosis and establish the grade and stage of the tumor. NMIBC can be categorized as low, intermediate and high risk. Low grade lesions are confined to the lining of the bladder. However, a significant proportion are considered intermediate and high risk for recurrence. Treatment of NMIBC is directed at reducing recurrences and preventing progression to a more advanced stage. For low grade lesions, local resection with or without adjuvant intravesicle chemotherapy or Bacillus Calmette-Guerin (BCG), and close follow up are usually successful in curing the disease, whereas high risk lesions should be treated with either adjuvant BCG or radical cystectomy. Recurrence overall for NMIBC is 30-70%, but for high-risk patients, 5-year recurrence rates are as high as 80%, with progression to muscle invasive disease in up to 50% of patients. An additional 10-15% will recur with metastatic disease. Following recurrence of NMIBC, few bladder-sparing options are available to prevent future recurrences and disease progression. Those with NMIBC that recurs following BCG and are unable or refuse surgery may be treated with pembrolizumab, which was approved for patients with carcinoma in situ (CIS) based on a complete response rate of 41% and a median duration of response of 16.2 months, or Adstiladrin, a non-replicating adenoviral vector-based gene therapy that was approved in 2022 for patients with Papillary or CIS BCG-unresponsive NMIBC based on a 51% response rate and median duration of response of 9.7 months. Recent data has been submitted to the FDA for N-803, an antibody cytokine fusion protein, showing a 71% response rate and 26.6 month duration of response for patients with BCG-unresponsive NMIBC, but only in the CIS subset, highlighting the need to provide the majority of patients with additional treatment options.

FGFR Inhibitors

Patients with somatic alterations in FGFR3 can be treated with FGFR inhibitors. Currently, the only FDA approved FGFR inhibitor for locally advanced or metastatic UC is erdafitinib, which received accelerated approval in the United States in 2019. In clinical trials, erdafitinib demonstrated a 32.2% overall response rate and a median duration of response of 5.4 months. We believe one of the key limitations to erdafitinib's duration of response is the emergence of mutations like the gatekeeper mutation. This same mutation may limit the efficacy of other first generation FGFR inhibitors such as infigratinib, pemigatinib and futibatinib in mUC. In a study of infigratinib and other FGFR inhibitors, the mutation that has been described in patients is the valine to methionine gatekeeper mutation at the V555 position of FGFR3, which results in a significant shift in potency of all of the first generation FGFR inhibitors. Once patients progress due to acquired drug resistance, there are very few options available, representing a significant unmet need in this patient population.



FGFR gatekeeper mutations block binding, resulting in a loss of potency in first generation FGFR inhibitors such as erdafitinib

Erdafitinib is a pan-FGFR inhibitor and due to its lack of selectivity, there are toxicities associated with the inhibition of FGFR receptors 1, 2 and 4. FGFR1 is expressed in kidney cells where it regulates phosphate and calcium reabsorption, and inhibition of FGFR1 results in hyperphosphatemia. Inhibition of FGFR2 can result in toxicities that significantly impact quality of life, such as dry mouth and stomatitis, skin, ocular and nail toxicities (e.g., oncholysis and hand-foot syndrome), and ocular toxicities such as keratitis and blurred vision. Inhibition of FGFR4 disrupts bile acid metabolism, and can result in diarrhea and liver toxicity. Hyperphosphatemia was a dose-limiting toxicity of erdafitinib and was reported in over 70% of patients in the Phase 2 clinical trial. Overall, adverse events resulted in 68% dose interruptions, 53% dose reductions, and 13 treatment discontinuations (in 99 patients). We believe the safety and tolerability profile of erdafitinib is a key limitation of its efficacy, as demonstrated by the dosing instructions to start at a daily 8mg dose, and only increase to 9 mg if hyperphophatemia is not observed. A similarly high rate of FGFR-related toxicities has been reported in clinical trials of other non-isoform selective FGFR inhibitors including pemigatinib, infigratinib and futibatinib.

Approximately 50-80% of NMIBC has been shown to carry FGFR3 gene alterations, the majority of which are activating point mutations. There are currently no targeted, approved therapies for FGFR3-driven NMIBC patients who have recurred following adjuvant BCG therapy. We believe that FGFR inhibitors have the potential to be highly efficacious in NMIBC, as suggested by three complete responses in four clinical trial patients at 7 weeks with NMIBC treated with infigratinib, nine complete responses in nine clinical trial patients at 3 months with high risk NMIBC treated with erdafitinib, and six complete responses in eight clinical trial patients with intermediate risk NMIBC at 3 months treated with erdafitinib in interim data posters presented at ASCO Genitourinary Cancer Symposium in February 2023. The safety and tolerability results were generally consistent with that known for erdafitinib, despite using a lower 6mg daily dose in this study. We believe a highly specific FGFR3-directed inhibitor, with minimal effects from other FGFR-related toxicities, could be highly efficacious and represent a potentially large future market opportunity for our product candidate in the approximately 50,000+ addressable patients with intermediate to high risk, FGFR3+ NMIBC seeking new treatment annually in the US.

We believe the limitations of current standard of care therapies, as well as the liabilities of first generation FGFR inhibitors, necessitates a solution that can address this unmet need and improve patient outcomes.

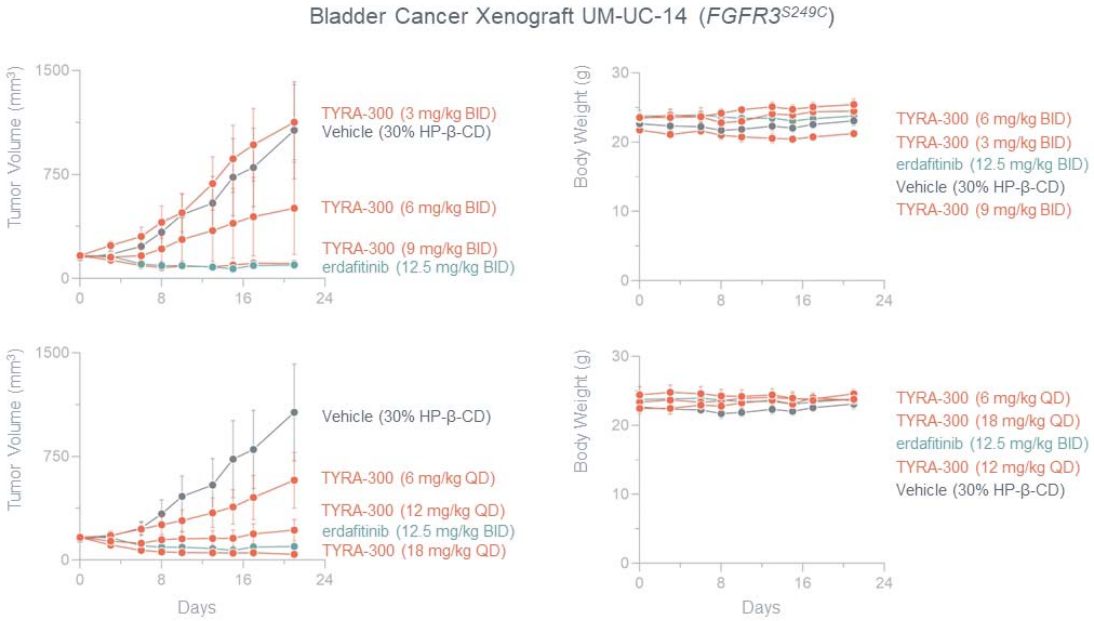
Our solution, TYRA-300

In November 2022, we initiated our Phase 1/2 clinical trial of TYRA-300, SURF301 (**S**tudy in **U**ntreated and **R**esistant **F**GFR3+ Advanced Solid Tumors), an international, multi-center, open label study designed to determine the optimal and maximum tolerated doses and the recommended Phase 2 dose of TYRA-300, as well as to evaluate the preliminary antitumor activity of TYRA-300.

In preclinical models to date, TYRA-300 has demonstrated potency against the gatekeeper mutation and selectivity for FGFR3. Although no head-to-head clinical studies have been conducted, we believe that these pre-clinical studies assist with the characterization of our product candidates and inform future clinical development.

TYRA-300 is active in a bladder cancer xenograft model

UM-UC-14 is a human bladder cancer cell line which contains an FGFR3 S249C activating mutation. TYRA-300 was tested in a preclinical mouse xenograft model using this cell line, as seen in the figure below. TYRA-300 given either once daily (QD) at a dose of 18 mg/kg or twice daily (BID) at a dose of 9 mg/kg led to substantial inhibition of tumor growth in this model. We observed 90% tumor growth inhibition (TGI) at the 9 mg/kg BID dose and 96% TGI at the 18 mg/kg QD dose. We observed 91% TGI with erdafitinib using a 12.5 mg/kg BID dose in this study.



TYRA-300 tumor growth inhibition in a UM-UC-14 xenograft model

Antitumor activity in the FGFR3 S249C activating mutant UM-UC-14 bladder cancer xenograft model in nu/nu mice of various doses of TYRA-300 (3, 6, and 9 mg/kg BID, upper left; and 6, 12, and 18 mg/kg QD, lower left) and erdafitinib (12.5 mg/kg BID) shown in both the upper and lower left. Body weight averages for the dose groups depicted in the upper and lower left are shown in the upper and lower right, respectively. All doses were by oral administration. No TGI was observed for TYRA-300 at 3 mg/kg BID. TGI observed for the other TYRA-300 doses is shown in parentheses; 6 mg/kg BID (53%), 9 mg/kg BID (90%), 6 mg/kg QD (46%), 12 mg/kg QD (80%), and 18 mg/kg QD (96%). We observed 91% TGI for 12.5 mg/kg BID erdafitinib. Data points represent mean tumor volume (n=6 per group except 6 mg/kg BID TYRA-300 dosing group where one animal was found dead at day 7 of treatment where n=5) and error bars represent standard error of the mean.

In this model, we used a salt form of TYRA-300, and the vehicle is 30% hydroxypropyl beta cyclodextrin (HP-ß-CD) for both the erdafitinib and TYRA-300 groups. Based on the results of this study, we expect to use a salt form of TYRA-300 for future TYRA-300 development. The salt form/cyclodextrin formulation used here replaces the polyethylene glycol 400 formulation we used in the bladder cancer xenograft model utilizing the RT112/84 +/- V555M immortalized cancer cell line, as described further below.

Potent inhibition of FGFR3 mutants including gatekeeper mutations

We utilized our SNÅP platform to design TYRA-300 to avoid any interactions with the gatekeeper region of FGFR3, which most other FGFR kinase inhibitors rely on for potency. In a bladder cancer xenograft model, we observed that we could obtain FGFR3 potency roughly equivalent to that of erdafitinib, by targeting other parts of the kinase active site. Although no head-to-head clinical studies have been conducted, this design strategy provides what we believe is a key advantage in that FGFR3 proteins containing gatekeeper mutations, such as V555M, were inhibited by TYRA-300 with very similar potency to wild-type FGFR3. Other FGFR inhibitors were at least 30-fold less potent versus FGFR3 V555M.

Enzymatic IC_{50} (nM) of TYRA-300 and other approved or late-stage clinical compounds

Kinase Domain	Alteration	erdafitinib	futibatinib	pemigatinib	infigratinib	TYRA-300
FGFR3 WT		0.6	2.3	1.3	2.0	1.6
FGFR3 [K650E]	A-loop Activator	1.0	3.7	3.9		2.8
FGFR3 [K650M]	A-loop Activator	1.4	5.9	9.6		2.3
FGFR3 [V555L]	Gatekeeper	19.7	175	206		1.5
FGFR3 [V555M]	Gatekeeper	90.6	1509	530	662	2.0

TYRA-300 has balanced potency for important gatekeeper and activating mutations

Ratios of Resistance Mutations Compared to Unmutated (Fold Difference in IC_{50})

FGFR3 [K650E]	A-loop Activator	1.7x	1.6x	3.0x		1.8x
FGFR3 [K650M]	A-loop Activator	2.3x	2.6x	7.4x		1.4x
FGFR3 [V555L]	Gatekeeper	33x	76x	159x		0.9x
FGFR3 [V555M]	Gatekeeper	151x	656.0x	408x	331x	1.3x

All assays run at Km of ATP for individual enzymes

Clinical and approved pan-FGFR inhibitors lose potency vs gatekeeper mutations

TYRA-300 retained potency against multiple potential acquired drug resistance mutations in FGFR3

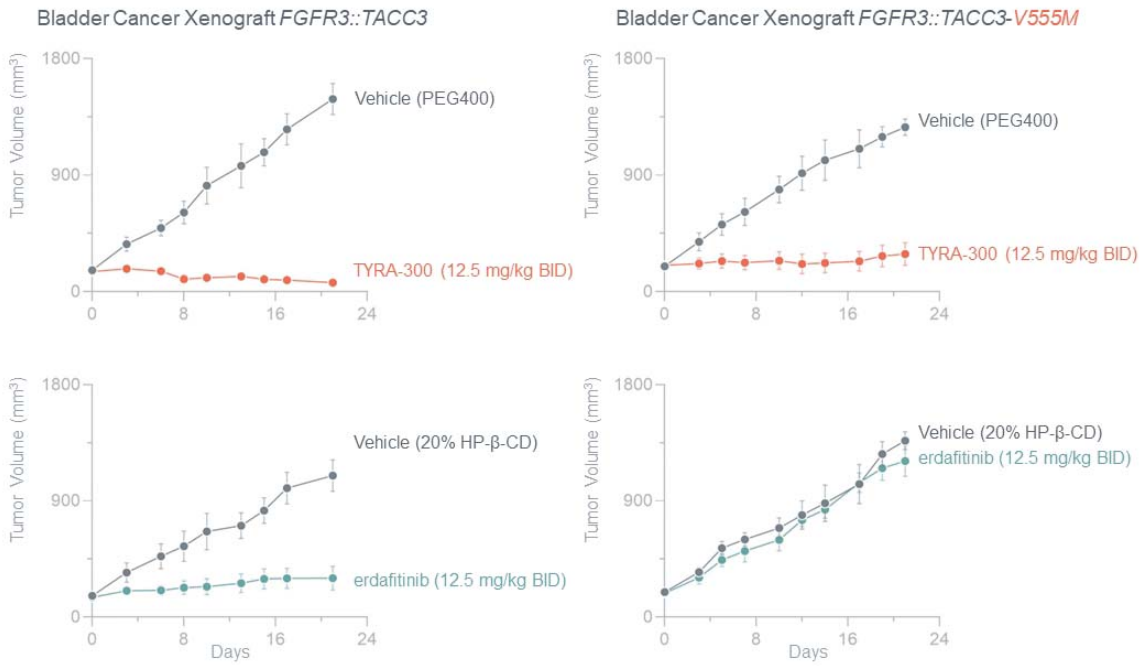
RT112/84 IC_{50} (nM) of TYRA-300 and other approved or late-stage clinical compounds

	erdafitinib	futibatinib	pemigatinib	infigratinib	TYRA-300
FGFR3-TACC3	4.4	11.0	5.3	14.5	7.9
FGFR3 [V555M]-TACC3	>3000	244	>3000	2557	18.0
WT / Mutant ratio	>682x	22x	>567x	177	2.3x

TYRA-300 maintains activity for key gatekeeper mutation in FGFR3 fusion clinical cell lines

TYRA-300 retained potency in a V555M CRISPR mutated RT112/84 immortalized cancer cell line

The ability of TYRA-300 to maintain potency against the V555M gatekeeper mutation, as observed in *in vitro* assays conducted to date, was tested in a preclinical xenograft model containing an FGFR3 fusion, as seen in the figure below. TYRA-300, at a dose of 12.5 mg/kg twice daily, led to significant inhibition of tumor growth in this model. We also observed inhibition of tumor growth by erdafitinib at a dose of 12.5 mg/kg twice daily in this model. We engineered a gatekeeper mutation into the cell line used for this model. We observed 77% inhibition of tumor growth by TYRA-300 in xenografts using the cell line containing the gatekeeper mutation, while we observed 12% tumor growth inhibition in the gatekeeper xenograft treated with erdafitinib.



TYRA-300 tumor growth inhibition was maintained in the presence of the FGFR3 V555M gatekeeper mutation in a RT112/84 xenograft model

Anti-tumor activity of TYRA-300 (95% TGI, upper left) and erdafitinib (73% TGI, lower left) dosed BID by oral administration in the FGFR3::TACC3 fusion activating RT112/84 bladder cancer xenograft model in Balb/c nude mice. Data points represent mean tumor volume (n=8 per group on left, n=6 per group on right) and error bars represent standard error of the mean. To test the effect of the gatekeeper mutation on tumor growth inhibition, we introduced the V555M mutation into the FGFR3::TACC3 fusion gene in the RT112/84 cell line using CRISPR. Anti-tumor activity in this isogenic gatekeeper containing model was evaluated using TYRA-300 (77% TGI, upper right) and erdafitinib (12% TGI, lower right) dosed BID by oral administration. The erdafitinib delivery vehicle in this experiment is 20% hydroxypropyl beta cyclodextrin and the TYRA-300 delivery vehicle is polyethylene glycol 400.

High selectivity for FGFR3

Designing inhibitors that bind to the ATP-binding site and can selectively differentiate between FGFR3 and FGFR1 is challenging due to the near-identical amino acid sequence in this site. We utilized the differentiated approach of our SNÅP platform to generate compounds, including TYRA-300, that capitalize on subtle conformational differences between FGFR3 and FGFR1 to obtain greater than ten-fold selectivity for FGFR3 versus FGFR1. In comparison, other FGFR inhibitors that are approved or in clinical development such as erdafitinib, pemigatinib, futibatinib and infigratinib, have demonstrated low or no selectivity for FGFR3. The high FGFR3-specificity that we observed to date for our potential product candidates for FGFR3 also extended to the broader family of protein kinases, where we showed that very few kinases were inhibited by our potential product candidates. Although we have not conducted any head-to-head clinical studies, we believe that TYRA-300's relative selectivity for FGFR3 observed in pre-clinical studies may address dose limiting toxicities of the first-generation compounds, enabling higher dosing and potentially better efficacy.

TYRA-300 selectivity vs. approved or late-stage clinical compounds: Ba/F3 Cellular IC_{50} (nM)

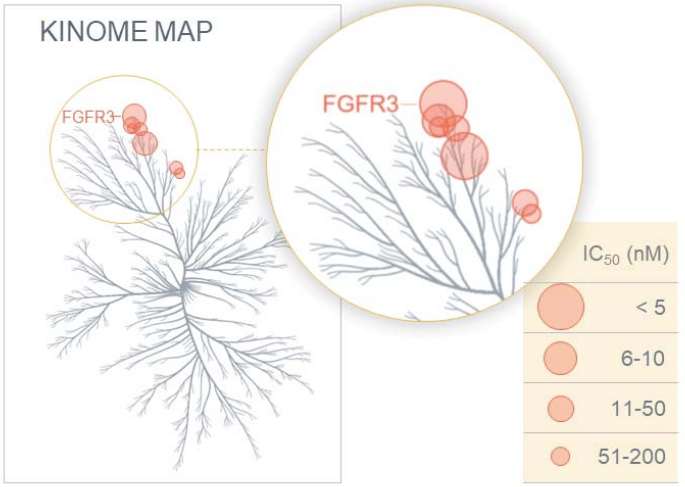
	erdafitinib	futibatinib	pemigatinib	infigratinib	TYRA-300
FGFR1	5.5	3.9	12.3	15.3	113
FGFR2	1.8	1.0	4.3	5.8	34.9
FGFR3	1.3	0.8	5.2	6.9	1.8
FGFR4	17.7	6.1	142	459	98.4

Fold Selectivity for FGFR3					
FGFR1	4.2x	4.9x	2.4x	2.2x	63x
FGFR2	1.4x	1.3x	0.8x	0.8x	19x
FGFR4	14x	7.6x	27x	67x	55x

TYRA-300 shows significant isoform selectivity for FGFR3 over other FGFR isoforms

TYRA-300 was highly selective for FGFR3 over other FGFR isoforms in a Ba/F3 cell-based assay

Beyond selectivity for FGFR3 relative to FGFR1, FGFR2 and FGFR4, TYRA-300 avoided off-target inhibition of other kinases when profiled in a scanMAX (KINOMEscan) screen.



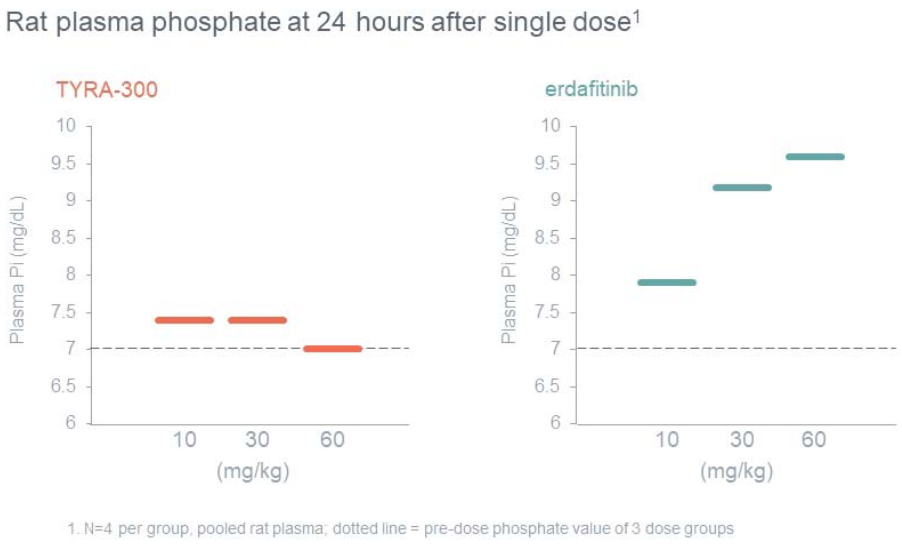
	TYRA-300	FGFR3 selectivity
FGFR3	1.6	1.0x
FLT4	2.1	1.3x
FGFR2	6.5	4.0x
FGFR4	11.0	6.9x
JAK2	35.5	22x
LTK	65.1	41x
FGFR1	108	68x
FLT1	201	126x
JAK3	206	129x

TYRA-300 was profiled in a scanMAX℠ (KINOMEscan) screen, IC_{50} data generated by Reaction Biology Inc.

TYRA-300 was highly selective for FGFR3 over other protein kinases

Phosphate levels in vivo

In a xenograft model using a bladder cancer-derived cell line RT112/84 shown above, treatment with TYRA-300 led to tumor regression at a dose of 12.5 mg/kg delivered twice a day. Treatment with erdafitinib also resulted in tumor volume reduction at the same dose in this model. Because the human dosing of erdafitinib is limited by hyperphosphatemia we measured the plasma phosphate levels in male Sprague Dawley rats 24 hours after dosing. Plasma phosphate levels in TYRA-300 treated rats were not substantially elevated at 10 mg/kg, 30 mg/kg, or 60 mg/kg doses, unlike the erdafitinib doses, as seen in the figure below. We believe TYRA-300 may be able to sustain higher doses without inducing hyperphosphatemia.



TYRA-300 did not elevate phosphate relative to erdafitinib

Effect of a single oral dose (10, 30 or 60 mg/kg) of TYRA-300 or erdafitinib on plasma phosphate levels 24 hours after dosing in male Sprague Dawley rats. Each data point represents the plasma phosphate measurement from the pooled sample of all 4 rats per dose group. Plasma phosphate levels were observed to be lower in the TYRA-300 treated groups than in the erdafitinib treated groups.

Clinical development plans for TYRA-300 in oncology

We submitted an IND to the FDA for TYRA-300 in June 2022 and received clearance in July 2022 to proceed with our Phase 1/2 clinical trial of TYRA-300, SURF301 (**S**tudy in **U**ntreated and **R**esistant **F**GFR3+ Advanced Solid Tumors), an international, multi-center, open label study designed to determine the optimal and maximum tolerated doses and the recommended Phase 2 dose of TYRA-300, as well as to evaluate the preliminary antitumor activity of TYRA-300. In November 2022, the first patient was dosed with TYRA-300 in SURF301.

We previously conducted IND-enabling studies for TYRA-300. In a completed 10-day non-GLP toxicology study in rats, TYRA-300 was well tolerated at dose levels up to 20 mg/kg in both males and females. We also conducted GLP toxicology studies in animals of TYRA-300 using the salt form/cyclodextrin formulation as part of our IND-enabling activities. TYRA-300 was well tolerated at dose levels up to 5 mg/kg daily in rats and doses up to 2 mg/kg daily in dogs for 28 days.

The Phase 1 portion of our SURF301 study has been designed as an accelerated dose escalation study and the primary objectives of the Phase 1 portion is evaluation of the safety and tolerability of TYRA-300, and to determine the optimal and maximum tolerated dose and the recommended Phase 2 dose (RP2D). In addition, we plan to characterize the pharmacokinetic/pharmacodynamic relationship for TYRA-300 as well as conduct early validation studies of a liquid biopsy companion diagnostic test to assist us in identifying appropriate patients for our product candidates.

We are designing the Phase 2 portion of our trial to be generally consistent with the well-established precedent of clinical trials of approved targeted therapies. If the data from any or all of these predefined patient populations are sufficient to support marketing authorization, we expect to seek feedback from the FDA in order to evaluate our ability to pursue and receive accelerated approval in the United States. We have not discussed any plans to pursue accelerated approval with the FDA, and there can be no assurance that after evaluation of the clinical trial results and/or feedback from the FDA, that we will decide to pursue accelerated approval or any other form of expedited development, review, or approval. We initially plan to evaluate TYRA-300 in the following three populations of FGFR3-positive tumors.

- Metastatic UC patients who have received an FGFR inhibitor previously and have developed resistance to that inhibitor due to an FGFR3 mutation, such as the gatekeeper V555M.

- Metastatic UC patients who have not yet received an FGFR inhibitor where we believe a reduction in toxicities and side effects, as well as the avoidance of the selection for the V555M gatekeeper mutations, have the potential to lead to improved tolerability, higher dosing and increasing the duration of responses.

- Any solid tumors containing known activating FGFR3 gene alterations.

Our future plans include potential combination studies with a PD-1/PD-L1, ADC's, or other novel agents in 1L and 2L mUC, where the risk of overlapping toxicities may be diminished when combined with TYRA-300. We could seek to initiate these studies as soon after we define the optimal Phase 2 dose and run them in parallel to initiation of the Phase 2 portion of SURF301. If our clinical data for TYRA-300 suggests differentiated safety and efficacy results, we will evaluate pursuing TYRA-300 as treatment in earlier bladder cancer settings (NMIBC), where minimizing side effects is a significant consideration for treatment choice and patient adherence. If we obtain positive efficacy results in mUC, we may decide to amend the SURF301 protocol to include a cohort of patients with FGFR3+ recurrent NMIBC. We believe that the full development potential for TYRA-300 may cover the entire spectrum of disease in urothelial cancer, and may represent a large opportunity relative to other drug targets given the high prevalence of FGFR3 mutations and the potential to treat earlier disease settings.

Our FGFR3 Program—TYRA-300 for Skeletal Dysplasias

Beyond oncology, mutations in FGFR3 are implicated in a family of skeletal conditions due to its role in regulating bone and cartilage formation. We believe that there is an opportunity to develop TYRA-300 or a second FGFR3 selective inhibitor to potentially address the long-term complications associated with these rare skeletal conditions including achondroplasia, hypochondroplasia, thanatophoric dysplasia, and other FGFR3-driven genetic syndromes.

Achondroplasia background

Achondroplasia, the most common form of dwarfism, is a skeletal dysplasia in which growth plate cartilage is affected, resulting in decreased growth of the long bones, vertebral bodies and skull base. These growth differences can result in health complications such as cranial and spinal stenosis, hydrocephalus, genu varum (bowed legs), and sleep apnea. A specific mutation in FGFR3, G380R, causes over 97% of achondroplasia. FGFR3 is expressed in growth plate chondrocytes (cartilage cells) where it functions in signaling pathways to limit growth. The G380R mutation, as well as other activating mutations, increase the activity of the FGFR3 protein, resulting in excessive limitation of growth causing these bones to be shorter than normal.

Achondroplasia is an autosomal dominant condition that occurs in approximately 1 in 15,000 to 40,000 newborns worldwide, and it is estimated that there are approximately 250,000 affected individuals worldwide and 3,000 affected individuals under the age of 18 in the US. Approximately 80% of achondroplasia cases arise through a spontaneous mutation of FGFR3, whereas 20% of cases are familial. While the heterozygous *FGFR3* mutation is rarely fatal, achondroplasia results in life-long health complications such as sleep apnea, obesity, recurrent ear infections, and bowed legs. The most serious sequelae include spinal stenosis (narrowing of the spinal canal); up to 20% of infants require surgery to address narrowing at the base of the skull (foramen magnum stenosis), which can be life-threatening; in adults, spinal stenosis of the lower back results in chronic pain, necessitating surgery and long-term pain management.

Current treatment for achondroplasia

In 2021, Voxzogo (vosoritide), a C-naturetic peptide analog that is a once daily injectable, was approved in the United States to increase linear growth in children with achondroplasia who are 5 years of age and older with open growth plates. In Europe, Voxzogo is approved to treat children with achondroplasia aged 2 and older with open growth plates. The pivotal study enrolled 120 children 5 to 15 years of age with genetically-confirmed

achondroplasia. They were randomized to receive either 15mcg/kg daily injections of Voxzogo or placebo for 52 weeks, followed by an open label extension study in which all children received Voxzogo. At the end of the 52 week treatment period, the children who received Voxzogo had an average linear growth velocity of 4.26cm/yr, translating to an increase from baseline of 1.57cm/yr greater than placebo. In a 10-person cohort in the Phase 2 study, 15mg/kg daily injection of Voxzogo achieved a mean growth velocity of 6.06cm/yr and a 2.01cm/yr change from baseline.

In 2022 and 2023, BridgeBio established clinical proof of concept for infigratinib, a daily oral FGFR1/2/3 inhibitor with phase 2 data in achondroplasia. In cohort 5 of the Phase 2 study, 10 evaluable children receiving a daily dose of 0.25 mg/kg achieved 6.77cm/yr average linear growth velocity and a 3.03cm/yr improvement over baseline. Based on this phase 2 data, BridgeBio has initiated the run-in portion of a phase 3 study.

Unmet need in achondroplasia and skeletal dysplasias

Long term health implication is key unmet need in Achondroplasia

While the approval of Voxzogo is an important milestone in the treatment of children with achondroplasia, the long-term therapeutic benefit of increasing growth velocity is not yet known. There are no long-term follow up data for Voxzogo to determine whether any of the health complications facing people with achondroplasia are alleviated. The daily delivery of Voxzogo can also be challenging for children and their parents. Voxzogo is supplied as a lyophilized powder that must be reconstituted in sterile water and injected daily into the skin. Injection site reactions, including swelling and redness, occurred in 85% of children; other complications include a risk of low blood pressure following injection. In addition, 35% of children developed anti-drug antibodies. While there was no association in the clinical trial with a decrease in linear growth velocity, it is not known if these antibodies might decrease the effectiveness of this treatment over longer periods of time.

There are other short-term and life-long complications such as cranial or spinal stenosis, hydrocephalus, cardiovascular events and sleep apnea associated with these skeletal dysplasia syndromes. Individuals may need to undergo surgery to correct spine or bone abnormalities and to reduce the pressure inside the brain in cases of hydrocephaly due to a narrow foramen magnum.

In rarer FGFR3-driven genetic syndromes such as thanatophoric dysplasia, another FGFR3-related skeletal condition, children often die in the neonatal period due to the severity of the skeletal abnormalities. As such, there remains a high unmet need for additional therapies that have the potential to address these conditions.

Opportunity for FGFR3 inhibitor in skeletal dysplasias

We believe that an oral, highly selective inhibitor of mutant FGFR3 may be highly desirable in pediatric achondroplasia because it could enable more convenient dosing and may have the potential to address long-term complications in affected individuals, including cranial or spinal stenosis, hydrocephalus and sleep apnea, alleviating the need for multiple painful surgeries and improving quality of life for this population. Additionally, a highly selective FGFR3 may have the ability to serve unmet needs of children with hypochondroplasia, thanatophoric dysplasia, other FGFR3-driven genetic syndromes and genetic short stature.

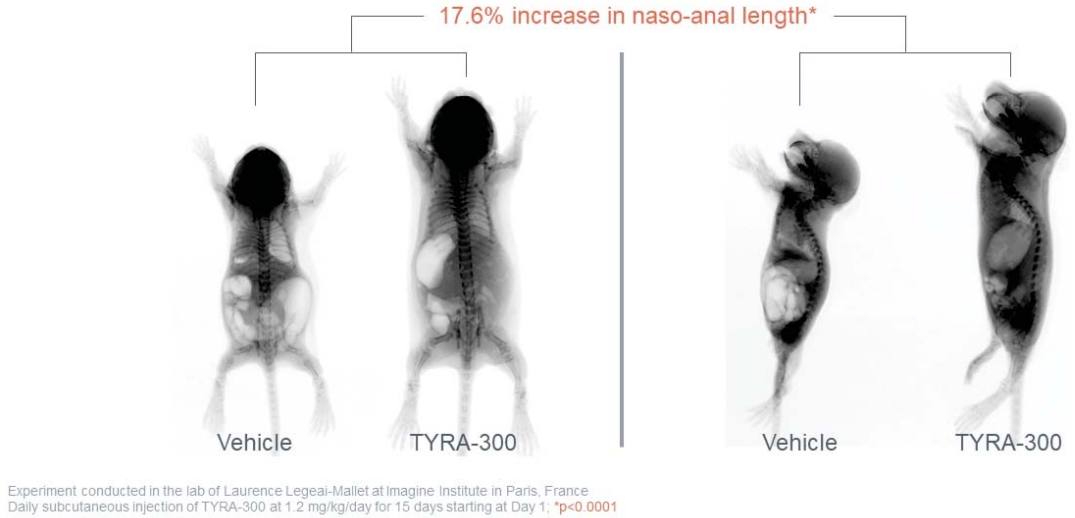
Our solution, TYRA-300

In March 2023, we announced we were expanding development of TYRA-300 into achondroplasia based on positive preclinical results demonstrated in a study performed in collaboration with the Imagine Institute in Paris, France.

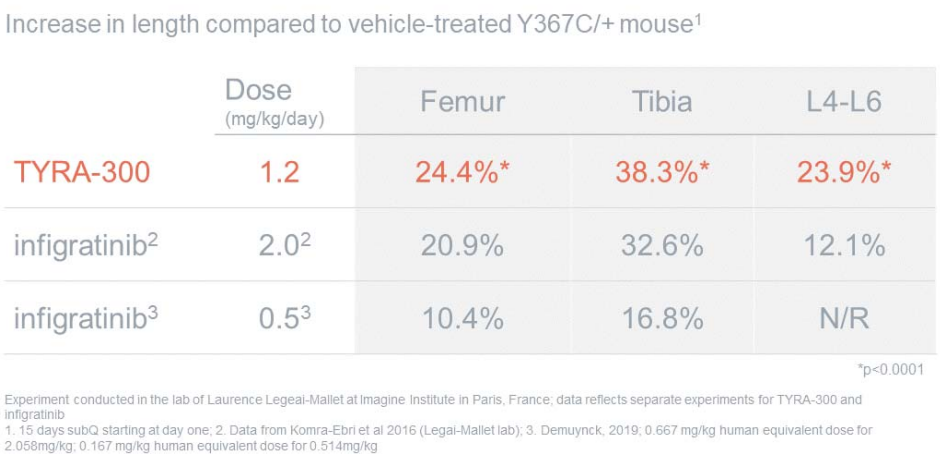
TYRA-300 has demonstrated selectivity for FGFR3 in preclinical models, as well as statistically significant increases in growth and bone length in the Imagine Institute FGFR3$^{Y367C/+}$ preclinical model. Although no head-to-head clinical studies have been conducted, we believe that these pre-clinical studies assist with the characterization of our product candidates and inform future clinical development.

TYRA-300 was active in a FGFR3$^{Y367C/+}$ preclinical model

TYRA-300 was studied in the Imagine Institute's FGFR3$^{Y367C/+}$ preclinical model. In the study, TYRA-300 was evaluated in FGFR3 wild-type and mutant preclinical models to measure increases in growth and bone length, compared to vehicle-treated mice. In an FGFR3$^{Y367C/+}$ model, TYRA-300 was administered daily at a 1.2 mg/kg dose for 15 days. TYRA-300 increased body length in mice by 17.6% compared to the vehicle ($p<0.0001$) and increased the length of the femur (+24.4%), tibia (+38.3%) and L4-L6 (+23.9%) in mice ($p<0.0001$).



TYRA-300 increased bone growth in FGFR3$^{Y367C/+}$model



TYRA-300 increased bone growth in FGFR3$^{Y367C/+}$model

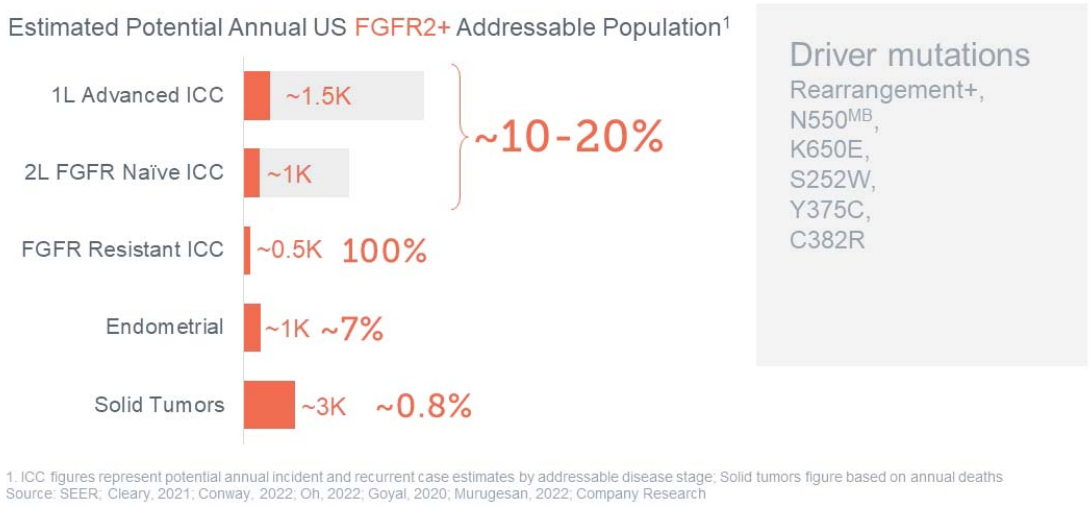
Development plans for TYRA-300 in Achondroplasia

We are planning additional IND-enabling studies and anticipate submitting an IND to the FDA to enable a Phase 2 study in pediatric achondroplasia in 2024. Additionally, we plan to evaluate development opportunities in hypochondroplasia, thanatophoric dysplasia, other FGFR3-driven genetic syndromes and genetic short stature.

Our FGFR2 program—TYRA-200

Our second product candidate, TYRA-200, is an FGFR1/2/3 inhibitor with potency against activating FGFR2 gene alterations, as well as clinically important molecular brake and gatekeeper resistance mutations. Similar to therapies designed for the treatment of FGFR3-driven cancers, resistance to both approved and investigational FGFR inhibitors has been shown to arise due to gene alterations in FGFR2. We have designed TYRA-200 to be active against multiple acquired resistant mutations that arise during treatment with other FGFR2 inhibitors. Although no head-to-head clinical trials have been conducted, we believe the use of comparative *in vitro* data from pre-clinical studies provides meaningful insight into the potential for TYRA-200 to improve on certain characteristics of approved and investigational FGFR inhibitors, and helps inform potential future clinical development of TYRA-200. We will study TYRA-200 initially in FGFR2-driven ICC resistant to previous FGFR inhibitors, and we may decide to pursue future studies (including combination studies) with a partner if we believe such a partnership could accelerate the development and/or maximize the market potential for TYRA-200. In December 2022, we submitted an IND to the FDA for TYRA-200 and received clearance in January 2023 to proceed with our Phase 1 clinical trial of TYRA-200. This trial is expected to dose the first patient in the second half of 2023.

ICC disease background

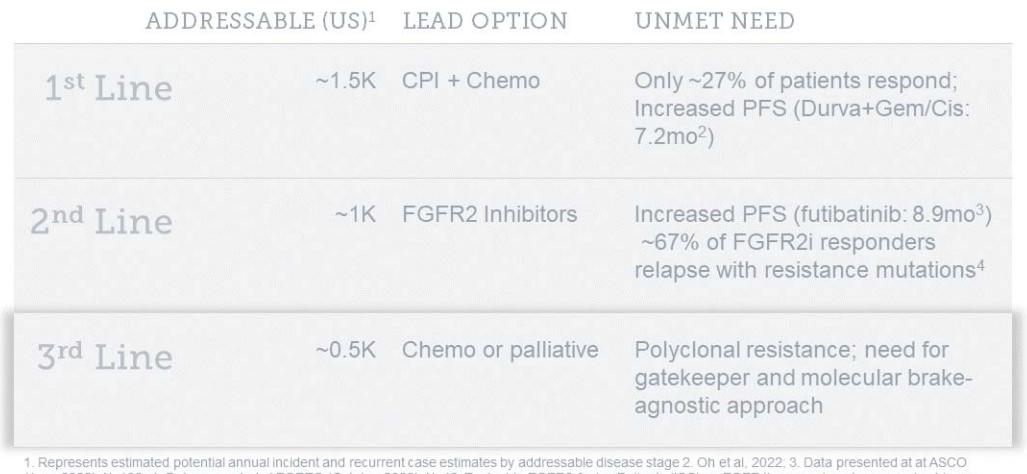


Potential patient populations for our FGFR2 inhibitor

ICC is a form of cancer that originates in the bile ducts, which are a series of thin vessels that transport bile from liver cells to the small intestine. Diagnosis of ICC is often difficult as it is not associated with any specific symptoms other than dull abdominal pain, weight loss, and elevated liver enzymes. ICC is a rare tumor, accounting for an estimated 10-20% of intrahepatobiliary cancers and an estimated ~11% of cancers of unknown primary origin. The median overall survival for all patients diagnosed with ICC is reported to be 16.1 months. The median overall survival for patients diagnosed with late-stage disease is less than one year.

FGFR2 is a protein receptor present on the cell surface that promotes cellular proliferation and transformation upon binding of fibroblast growth factor. Similar to FGFR3, activating gene alterations of FGFR2 have been implicated in the tumorigenesis of multiple solid tumor types. Approximately 15-20% of patients with ICC have genetic alterations in FGFR2, which are primarily gene rearrangements and activating mutations. In addition to ICC, FGFR2 drives and estimated ~7% of endometrial cancers and 0.8% of other solid tumors.

Standard of care and current limitations for the treatment of Advanced ICC



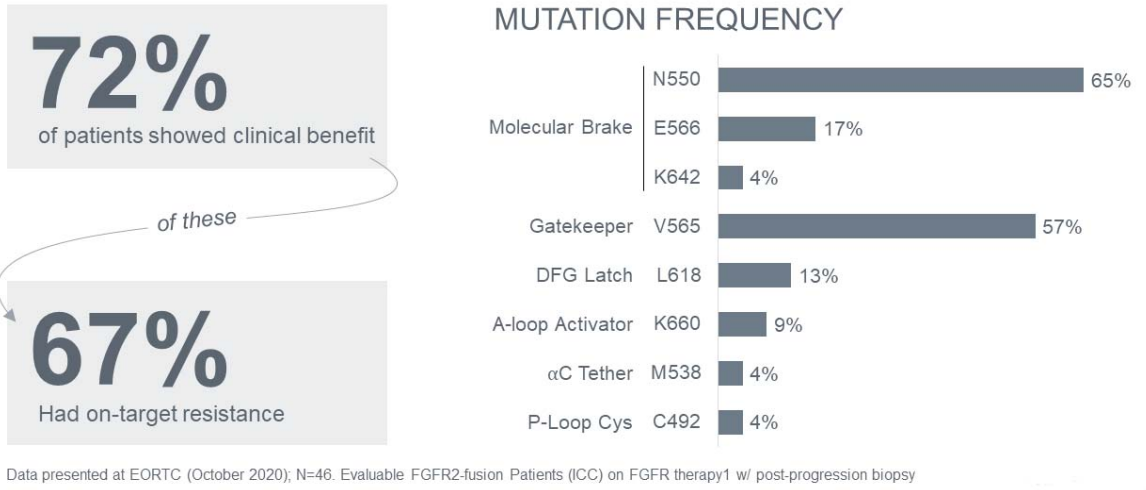
Acquired resistance is a key unmet need in FGFR2+ ICC

Currently, surgical recession is the only curative option available to ICC patients. However, only up to one-third of patients are eligible for surgery at diagnosis and up to 70% of patients experience a recurrence largely within the first two years following surgery. Patients with unresectable tumors are typically treated with systemic therapies. The previously recommended frontline regimen was a combination of gemcitabine and cisplatin, which offered a median overall survival benefit of 11.7 months. A recent Phase 3 study demonstrating statistically significant median overall survival benefit for the combination of durvalumab with gemcitabine and cisplatin vs gemcitabine plus cisplatin (12.8 months [95% CI 11.1, 14) vs 11.5 months [95% CI 10.1, 12.5]) led to an approval in previously untreated unresectable or metastatic biliary tract cancer in September 2022. A second Phase 3 study comparing pembrolizumab plus gemcitabine and cisplatin vs gemcitabine and cisplatin also reported a statistically significant overall survival benefit, though the details of the study have not been made public. The results from these two studies firmly establish a role for immunotherapy in combination with cisplatin-based chemotherapy as a new standard of care in 1L cholangiocarcinoma. Upon disease progression, patients with actionable mutations, such as IDH1/IDH2 and *FGFR2* alterations, are eligible to receive targeted therapies.

FGFR inhibitors

Patients with somatic alternations in *FGFR2* are eligible to be treated with Pemazyre (pemigatinib), a pan-FGFR inhibitor that received accelerated approval in the United States in 2020 for treatment following chemotherapy. In the Phase 2 clinical trial of pemigatinib for the treatment of ICC, the overall response rate was 36% (95% CI 27, 45) with a median duration of response of 9.1 months (95% CI 6.0, 14.5). A second pan-FGFR inhibitor, Truseltiq (infigratinib), received accelerated approval in the United States in 2021 based on an overall response rate of 23% (95% CI 16, 32) and a median duration response of 5.0 months (95% CI 3.7, 9.3). It was subsequently announced in October 2022 that infigratinib would be withdrawn from the market and no longer be developed in oncology indications. A third pan-FGFR inhibitor, futibatinib, received accelerated approval for ICC with FGFR2 gene fusions or rearrangements in September 2022 on the basis of a single arm study that showed an ORR of 42% (95%CI 32, 52) and a median duration of response of 9.7 months (95% CI 7.6, 17.1). The investigational FGFR2-specific inhibitor RLY-4008 has reported remarkable response rates in a small dataset of patients who have not received an FGFR inhibitor previously, though RLY-4008 and the multi-kinase inhibitor TT-00420 have shown limited activity in patients whose tumors have developed these acquired resistance mutations.

We believe the critical unmet need for patients with FGFR2 fusion or FGFR2-altered ICC is balancing the potency for the wild type and the numerous on-target resistance mutations that emerge in patients treated with currently approved and investigational FGFR inhibitors. The most frequently occurring acquired drug resistance mutations are active site mutations such as the gatekeeper and amino acids comprising the molecular brake. These mutations, as well as allosteric gain-of-function mutations, have been observed clinically to confer resistance to the currently approved FGFR inhibitors. We believe maintaining potency against all of these clinically important mutations as well as wild-type FGFR2 could potentially improve efficacy and duration of response.



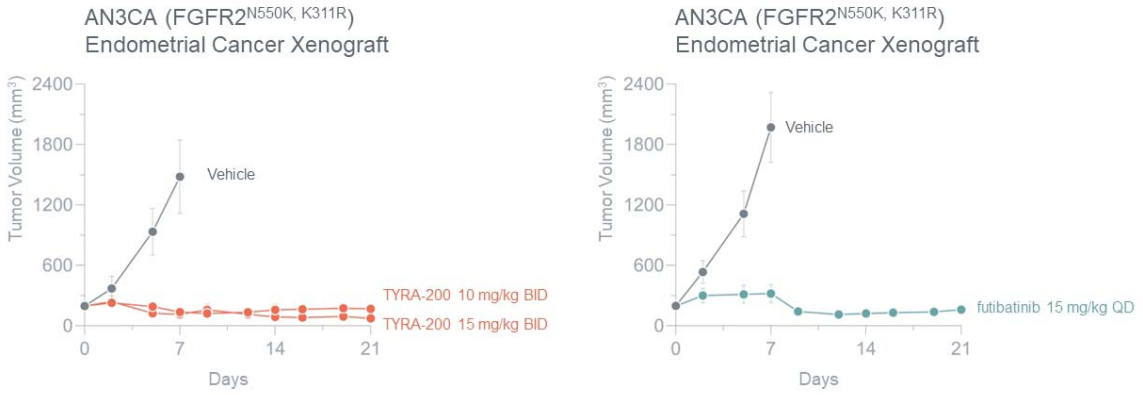
Acquired drug resistance is common in patients with ICC treated with FGFR inhibitors

Our solution, TYRA-200

In preclinical models to date, TYRA-200 has demonstrated potency against gatekeeper, molecular brake, and A-loop activator mutations and selectivity for FGFR1-3 over FGFR4. Although no head-to-head clinical studies have been conducted, we believe that these pre-clinical studies assist with the characterization of TYRA-200 and inform future clinical development.

TYRA-200 is active in an FGFR2 driven endometrial cancer xenograft model

AN3CA is a human endometrial cancer cell line which contains an FGFR2 N550K activating mutation. TYRA-200 was tested in a preclinical mouse xenograft model using this cell line, as seen in the figure below. TYRA-200 given BID at a dose of 10 mg/kg or 15 mg/kg BID led to substantial inhibition of tumor growth in this model. We observed TGI with futibatinib using a 15 mg/kg QD dose in this study.



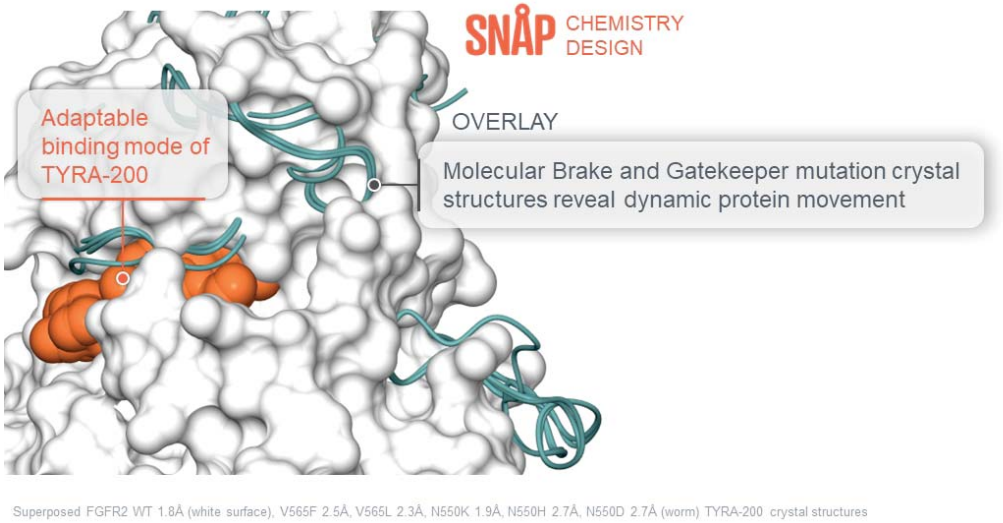
TYRA-200 tumor growth inhibition in a AN3CA xenograft model

Antitumor activity in the FGFR2 N550K, K311R mutant AN3CA endometrial cancer xenograft model in nu/nu mice of various doses of TYRA-200 (10 and 15 mg/kg BID, left) and futibatinib (15 mg/kg QD, right). All doses were by oral administration. Regression, calculated as % Regression (for $\Delta T<0$) = $100*(\Delta T/T_0)$, observed for TYRA-200 10 mg/kg BID is 14%, and for 15 mg/kg BID is 56%. We observed 5% regression with 15 mg/kg QD futibatinib. The vehicle for TYRA-200 is 30% hydroxypropyl beta cyclodextrin, and the vehicle for futibatinib is 0.5% hydroxypropyl

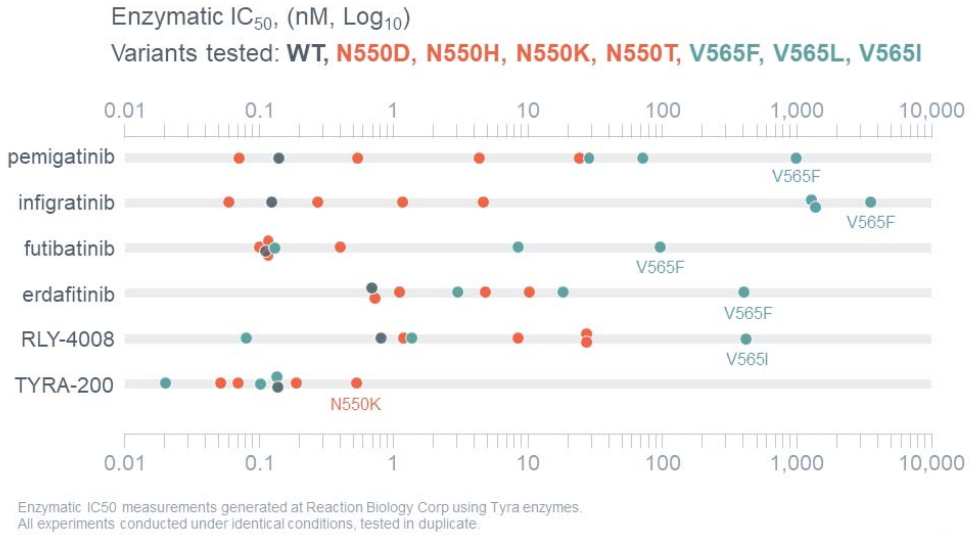
methylcellulose with 0.2% tween 80. Data points represent mean tumor volume (n=6 per group) and error bars represent standard error of the mean.

Potent inhibition of FGFR2 mutants including gatekeeper, molecular brake, and A-loop activator mutations

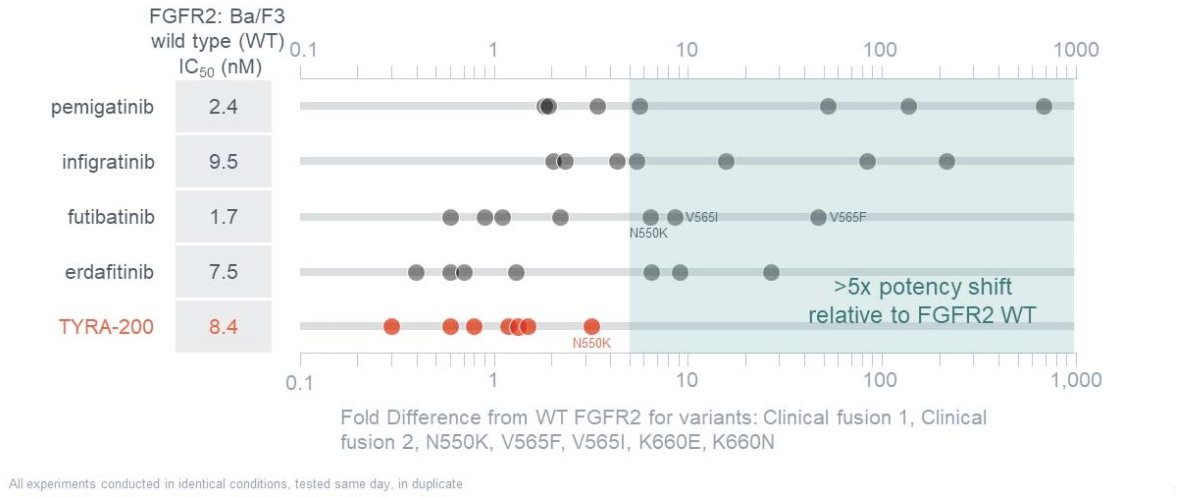
We utilized our SNÅP platform to design TYRA-200 to retain potency for a variety of acquired resistance mutations that alter FGFR2 protein structure and consequently can affect inhibitor potency. In preclinical models conducted to date, TYRA-200 has demonstrated similar potency in FGFR2-driven Ba/F3 cells to erdafitinib, pemigatinib, futibatinib or infigratinib, while reducing or eliminating the decrease in potency observed with N550K/H/D and E566A molecular brake, V565F/L/I gatekeeper, and K660E/N A-loop activator resistance mutations.



Acquired resistance mutations alter FGFR2 protein structure

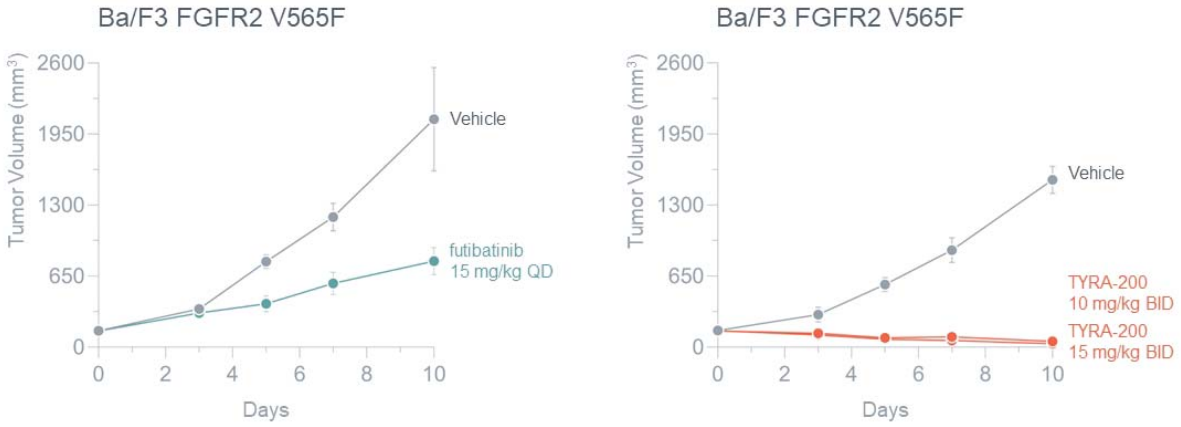


TYRA-200 retained potency against multiple potential acquired drug resistance mutations in FGFR2



TYRA-200 retained potency against multiple acquired drug resistance mutations in FGFR2-driven Ba/F3 cell lines

The potential of TYRA-200 to maintain potency against the V565F gatekeeper mutation, a key liability of pemigatinib, infigratinib, futibatinib, and erdafitinib as observed in *in vitro* assays conducted to date, was tested in a preclinical allograft model of an FGFR2-driven Ba/F3 cell line with the V565F gatekeeper mutation as seen in the figure below. We observed 96% and 98% inhibition of tumor growth by TYRA-200 in the allograft, while we observed 62% tumor growth inhibition in the allograft treated with futibatinib.

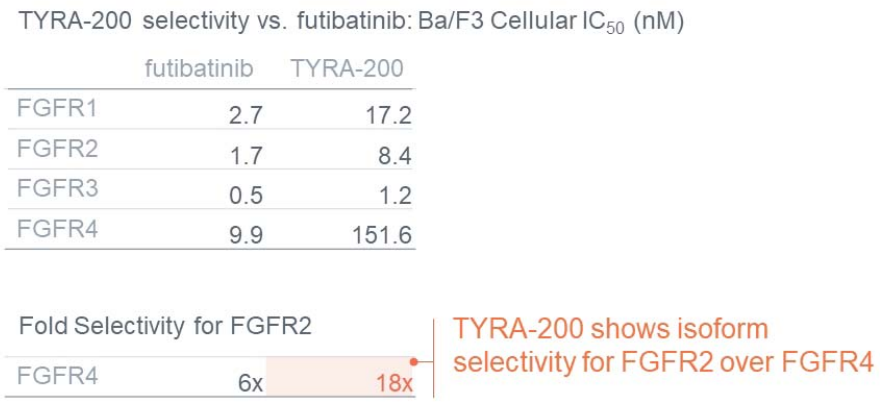


TYRA-200 tumor growth inhibition was maintained in the presence of the FGFR2 V565F gatekeeper mutation in a Ba/F3 FGFR2 allograft model

Antitumor activity in the Ba/F3-FGFR2 V565F gatekeeper mutant model in nu/nu mice of various doses of TYRA-200 (10 and 15 mg/kg BID, left) and futibatinib (15 mg/kg QD, right). All doses were by oral administration. TGI observed for TYRA-200 10 mg/kg BID is 96%, and for 15 mg/kg BID is 98%. We observed 62% TGI for 15 mg/kg QD futibatinib. The vehicle for TYRA-200 is 30% hydroxypropyl beta cyclodextrin, and the vehicle for futibatinib is 0.5% hydroxypropyl methylcellulose with 0.2% tween 80. Data points represent mean tumor volume (n=6 per group) and error bars represent standard error of the mean.

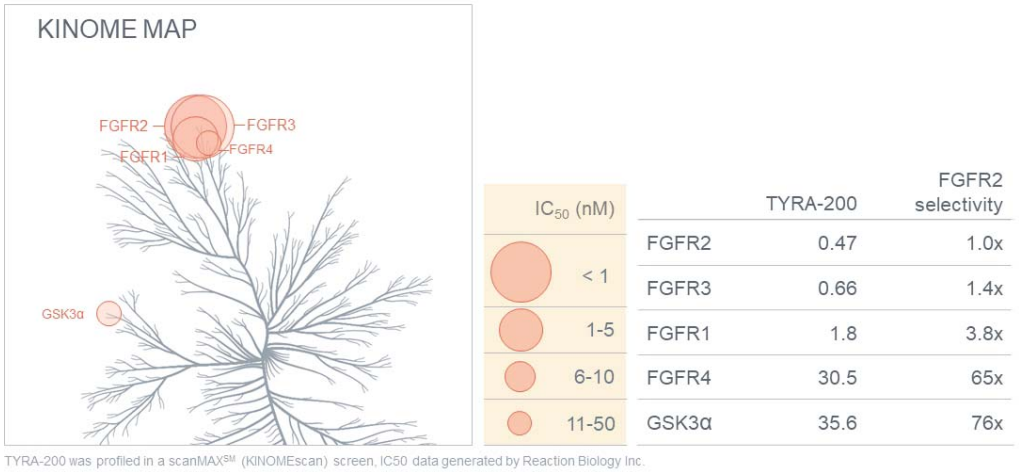
Selectivity for FGFR1/2/3 vs FGFR4

Designing covalent inhibitors that bind to the ATP-binding site and selectively differentiate between FGFR2 and other isoforms is challenging due to the near-identical amino acid sequence in this site. We utilized the differentiated approach of our SNÅP platform to generate compounds, including TYRA-200, that capitalize on subtle conformational differences between FGFR4 and the other isoforms to obtain greater selectivity for FGFR1-3 versus FGFR4. In comparison, the covalent FGFR inhibitor futibatinib has demonstrated lower selectivity for FGFR4, which may point to a potential to be dose limited by FGFR4-related toxicities such as diarrhea and liver toxicity. In clinical studies of futibatinib, the dose limiting toxicity in Phase 1 was Grade 3 elevation of liver function tests in 3 of 9 patients at 24mg. In the Phase 2 registration study in ICC, Grade 3 liver enzyme abnormalities were observed in 7 to 13% of patients and 39% of patients experienced diarrhea of any grade at a dose of 20mg daily. The selectivity for FGFR1-3 vs FGFR4 that we observed for TYRA-200 also extended to the broader family of protein kinases, where we observed that very few kinases were inhibited. Although we have not conducted any head-to-head clinical studies, we believe that TYRA-200's relative selectivity for FGFR1-3 relative to FGFR4 observed in pre-clinical studies may result in improved tolerability with respect to futibatinib.



TYRA-200 was selective for FGFR1-3 over FGFR4 in a Ba/F3 cell-based assay

Beyond selectivity over FGFR4, TYRA-300 avoided off-target inhibition of other kinases when profiled in a scanMAX (KINOMEscan) screen.



TYRA-200 was highly selective for FGFR2 over other protein kinases

Development plans for TYRA-200

In December 2022, we submitted an IND to the FDA for TYRA-200 and received clearance in January 2023 to proceed with our Phase 1 clinical trial of TYRA-200. We will study TYRA-200 initially in FGFR2-driven ICC resistant to previous FGFR inhibitors. We expect to dose the first patient in this trial in the second half of 2023. The currently approved pan-FGFR inhibitors as well as several investigational agents are not active against the entire spectrum of clinically important acquired resistance mutations that develop in response to FGFR inhibition. Polyclonal resistance (multiple resistance mutations that occur in the same patient) is a common feature in this patient population, and the ability to demonstrate clinically beneficial activity in this setting will provide proof of concept and validate the design principles behind TYRA-200. These data would provide confidence in our belief that addressing acquired resistance may prolong the duration of responses, and ultimately PFS, in the FGFR-naive setting, and confirm our belief that TYRA-200 is highly differentiated in the competitive landscape of FGFR inhibitors. Beyond FGFR-resistant and FGFR-naive ICC, there is potential for TYRA-200 to extend into metastatic endometrial carcinoma, where up to 7-16% of patients have FGFR2 mutations, of which 25% are N549 molecular brake activating mutations. Additional FGFR2-driven patient populations in advanced colorectal, breast, ovarian, gastric, and lung cancer will also be evaluated in a tumor agnostic fashion.

Our FGFR4/FGF19 discovery program

FGFR4 is expressed broadly in normal tissues, including lung, liver, and the GI tract. FGFR4 as an oncology target has been primarily studied in hepatocellular carcinoma, where it is the cell surface receptor for FGF19 with β-klotho. Approximately 30% of HCC cases are thought to be dependent on FGFR4 signaling due to amplification of FGF19. Several FGFR4 selective inhibitors have been developed and evaluated in the clinic with limited success. These covalent inhibitors are highly selective for FGFR4 vs the other FGFR family members due to their targeting of an FGFR4-specific cysteine. However, clinical activity was limited by low response rates, short duration of responses, and toxicity due to the dysregulation of normal bile acid synthesis.

Role of FGFR4/FGF19 in cancer

FGFR4 is involved in the transduction of key signals essential for cellular proliferation and survival. Aberrant activation of the FGFR4 pathway is observed in multiple malignancies, most notably in approximately 30% of hepatocellular carcinoma. It is also implicated as a driver in approximately 7.5% of pediatric rhabdomyosarcomas, in breast cancer cases, and less commonly in other select solid tumors.

The role of FGFR4 in cancer has been best described in hepatocellular carcinoma. In normal hepatocytes, FGFR4 regulates bile acid synthesis and hepatocyte proliferation in response to fibroblast growth factor 19 (FGF19). FGF19 is a post-prandial enterohepatic hormone that signals through FGFR4 and its associated co-receptor Klotho-b (KLB) to exert its normal cellular functions. In certain cancers, such as HCC and breast cancer, FGF19 is aberrantly expressed due to focal chromosomal amplifications or epigenetic mechanisms, promoting tumor cells to become dependent on the FGFR4/KLB/FGF19 oncogenic axis.

Currently there are currently no approved therapies that selectively target the FGFR4-FGF19 axis. A successful approach would represent the introduction of a first-in-class targeted therapy in HCC.

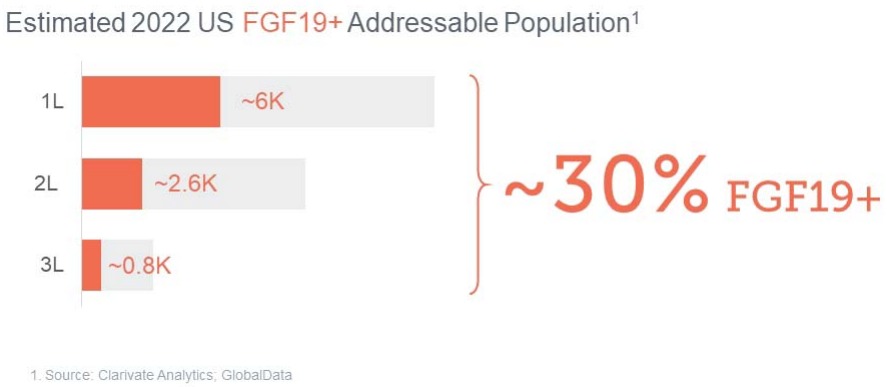
Pan FGFR inhibitors have been previously studied in FGFR4-driven malignancies, such as HCC. Development of erdafitinib was initiated in HCC and subsequently discontinued, while futibatinib is currently being studied in combination with immunotherapy in a FGF19-selected population in HCC. However, these approaches have been constrained in other indications by the dose-limiting toxicities elicited by off-target inhibition of FGFR1 and FGFR2.

Previous attempts to selectively target FGFR4 resulted in sub-optimal responses with short durations. Clinical studies with the FGFR4-selective inhibitors fisogatinib and roblitinib demonstrated the potential of targeting FGFR4 in HCC patients whose tumors expressed FGF19. While the overall response rates of 17% and 21%, respectively, provided clinical proof-of-concept, the durability was short and acquired drug resistance was observed in some cases.

Results from the fisogatinib study led to the identification of FGFR4 mutations known to interfere with drug activity. These mutations included V550 gatekeeper mutations and C552 mutations, both of which were found to cause a loss of fisogatinib potency of more than 1,000-fold.

Our FGFR4/FGF19 Program

Our FGFR4 drug discovery efforts are driven by our deep structural understanding of the FGFR family including over 70 co-crystal structures of FGFR4 itself. We are seeking to develop a FGFR4 inhibitor that is agnostic to acquired resistance mechanisms originating from the V550 gatekeeper and the C552 mutations, as well as other potential FGFR-driven compensatory mechanisms. We anticipate that our product candidate will also have potential for antitumor activity in patients with spontaneous FGFR4 activating mutations at the gatekeeper (V550), as well as in rare FGFR4 fusions.



Potential patient populations for our FGFR4 inhibitor

Our RET discovery program

RET is a cell surface RTK expressed in a variety of normal tissues such as lung, skin, brain, and endocrine organs. Mutations in RET, including gene rearrangements/fusions and point mutations, can serve as oncogenic drivers in tumors. The tumorigenic role RET have been well characterized across multiple malignancies, leading to strong interest as a target for precision drug development.

Several RET inhibitors are currently indicated for the treatment of RET-mutated cancers. Gavreto (pralsetinib) is currently indicated under an accelerated approval for adults with metastatic RET fusion-positive NSCLC, while Retevmo (selpercatinib) is indicated under a full approval for patients with RET fusion-positive metastatic NSCLC. Both selpercatinib and pralsetinib also retain indications under accelerated approval in adult and pediatric patients 12 years of age and older with advanced or metastatic medullary thyroid cancer with a *RET* mutation and metastatic thyroid cancer with a *RET* gene fusion. In 2022, selpercatinib additionally achieved accelerated approval for treatment of adult patients with locally advanced or metastatic solid tumors with a *RET* gene fusion that have progressed on or following prior systemic treatment.

Prevalence of RET alterations in cancer

RET is essential for neuronal and embryonic development. Activating genetic alterations such as gene fusions and point mutations in RET are oncogenic. In non-small cell lung cancer (NSCLC) and papillary thyroid carcinoma (PTC) RET gene fusions lead to constitutive activation and oncogenesis. In NSCLC, 1 to 2% of patients who are negative for mutations or rearrangements in other common oncogenic drivers such as EGFR, ERBB2, BRAF, KRAS and ALK, have RET fusions. In PTC, the most common form of thyroid cancer, an estimated 35% of cases in North America and up to 65% of cases in other geographies are associated with RET fusions. In sporadic medullary thyroid carcinoma (MTC), up to 70% of patients have activating mutations in RET, whereas in familial cancer syndromes, such as MEN2B, germline RET mutations at M918T predispose carriers to MTC.

Limitations of current RET inhibitors

The first FDA approved therapies for RET-driven tumors were Caprelsa (vandetanib) and Cabometyx (cabozantinib), both of which are multi-kinase inhibitors approved for MTC that has progressed on standard therapy or is symptomatic and in need of treatment. Selpercatinib and pralsetinib are highly specific next-generation RET inhibitors that have received accelerated approval in patients with RET-dependent tumors including NSCLC, PTC and MTC.

Both vandetanib and cabozantinib were approved in MTC without a restriction to the RET-mutated population. For patients with MTC with activating RET mutations treated with these therapies, secondary resistance mutations at the gatekeeper position V804 arise during treatment and can be identified at the time of disease progression. Selpercatinib and pralsetinib address a key liability of the first-generation multi-kinase inhibitors at V804. In metastatic RET-fusion positive patients with NSCLC that had previously failed platinum-based chemotherapy, selpercatinib treatment led to a 62% response rate with a median duration of response of 17.5 months. In patients with treatment-naïve NSCLC, the overall response rate was 84%. An overall response rate of approximately 69% was observed in RET-mutant MTC regardless of whether patients had previously failed on other kinase inhibitor therapies. Roughly similar efficacy was observed in clinical trials with pralsetinib. Both selpercatinib and pralsetinib received accelerated approval in the United States in 2020.

Although selpercatinib and pralsetinib were only approved in 2020 and therefore do not have a long history of use, the emergence of acquired drug resistance mutations has already been observed at the G810 solvent front. Based on the observed history with other targeted therapies in molecularly defined subgroups, we believe the use of these drugs will likely lead to additional resistance liabilities over time.

Our RET Program

We are developing a RET-specific inhibitor that is designed to retain potency for the V804 gatekeeper and the G810 solvent front mutations. Our drug discovery efforts are driven by our ability to gain molecular-level detail and insights from internally derived co-crystal structures of selpercatinib, pralsetinib and other inhibitors bound to RTKs. Recent publications have shown that these inhibitors have liabilities at the gatekeeper, the solvent front, or other parts of the ATP-binding pocket. Our focus is to develop RET inhibitors that address many of these key liabilities, an approach which we believe will allow our product candidates to demonstrate antitumor activity in patients who progress on current-generation RET inhibitors.

Our initial development plans for our RET inhibitor product candidate will focus on patients who fail previous treatment with a RET inhibitor due to acquired mutations in V804 or G810. We anticipate that our RET inhibitor will also have potential for antitumor activity in patients with RET treatment-naïve containing RET fusions or RET activating mutations, representing approximately 5,000 patients across NSCLC, PTC and MTC.

With regard to all of our programs, we may consider entering into a strategic partnership on an opportunistic basis if we believe that such a partnership can accelerate the development and/or maximize the market potential of the particular program.

Competition

The pharmaceutical and biotechnology industries are characterized by rapidly advancing technologies, intense competition, and a strong emphasis on proprietary products. While we believe that our technology, technical expertise, and drug development experience provide us with competitive advantages, we face increasing competition from many different sources, including pharmaceutical and biotechnology companies, academic institutions, governmental agencies, and public and private research institutions. Product candidates that we successfully develop and commercialize may compete with existing and/or new therapies that may become available in the future.

Many of our competitors, either alone or with their collaborators, have significantly greater financial resources, established presence in the market, expertise in manufacturing, R&D, pre-clinical activities and clinical trial conduct. Additionally, many of our competitors are commercial-stage entities with experience in obtaining regulatory approvals and reimbursement for marketed approved products. These competitors also compete with us in recruiting and retaining qualified scientific and management personnel, establishing clinical trial sites and patient registration for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs. Smaller or early-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with larger and/or established companies. Additional mergers and acquisitions may result in even more resources being concentrated in our competitors.

Our commercial potential could be reduced or eliminated if our competitors develop and commercialize products that are more effective, have a more favorable safety profile, and are more convenient or less expensive than products that we may develop. Our competitors also may obtain FDA or other foreign regulatory approval(s) for their products more rapidly than us, which could result in our competitors establishing a strong market position before we are able to enter the market or could otherwise make our development more complicated. We believe the key competitive factors affecting the success of all of our programs are likely to be efficacy, including duration of human response and breadth of coverage, safety and patient convenience.

There are numerous companies developing or marketing treatments for cancer, including many major pharmaceutical and biotechnology companies. These treatments consist of small molecule drug products, biologics, cellular therapies, and traditional chemotherapy. Currently, there are three FGFR inhibitors indicated for the treatment of adults with previously treated, unresectable locally advanced or metastatic cholangiocarcinoma with a *FGFR2* fusion or other rearrangement: Incyte Corporation's Pemazyre (pemigatinib), Helsinn Healthcare, SA's Truseltiq (infigratinib), and Taiho Oncology's Lytgobi (futibatinib). These indications are approved in the US under accelerated approval based on overall response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s). Similarly, Janssen Biotech, Inc's Balversa (erdafitinib) is currently indicated under an accelerated approval for the treatment of adult patients with locally advanced or metastatic UC that has eligible *FGFR2* or *FGFR3* gene alterations and have progressed during or following at least one line of platinum-containing chemotherapy.

Incyte Corporation is currently conducting a confirmatory Phase 3 clinical study in treatment-naïve, metastatic unresectable cholangiocarcinoma (NCT03656536). While Taiho is also pursuing a randomized study in frontline cholangiocarcinoma (NCT04093362), a separate confirmatory trial is slated to begin in 2023 in patients with previously-treated, locally advanced or metastatic unresectable cholangiocarcinoma (NCT05727176). In late 2022, Helsinn Healthcare SA issued a notice of permanent discontinuation of distribution of Truseltiq (infigratinib) effective March 31, 2023, thus ending all promotional and educational activities.

Janssen is pursuing a randomized confirmatory study of erdafitinib in previously-treated patients diagnosed with mUC (NCT03390504). This study is expected to report results later in 2023, which may affect the Phase 2 and Phase 3 development plans for TYRA-300. In addition, Janssen is studying erdafitinib in NMIBC (NCT04917809, NCT04172675) and recently reported results that provide an important read-through for TYRA-300. At the 2023 ASCO Genitourinary Symposium, Janssen reported high complete response rates in both high- and intermediate-risk population of NMIBC, but toxicities were significant, even with a lower dose. Tyra believes these data provide proof of concept that an oral FGFR3-selective inhibitor with a better tolerability profile can demonstrate substantial benefit in these earlier disease settings.

There are a number of FGFR-isoform selective inhibitors in development for oncology as well. In January 2022, the FDA cleared the IND for Kinnate Biopharma Inc.'s product candidate KIN-3248, an FGFR2/3 inhibitor being developed for ICC and UC (NCT05242822). Relay Therapeutics, Inc.'s FGFR2-specific inhibitor RLY-4008 is currently in Phase 1 with stated plans to develop their candidate in ICC (NCT04526106). Lilly's Loxo Oncology recently initiated a Phase 1 study in mUC for LOXO-435 (LOX-24350), an isoform-selective FGFR3 inhibitor compound (NCT05614739).

In 2021, BioMarin Pharmaceutical's Voxzogo, a once daily injectable C-naturetic peptide (CNP) analog was granted accelerated approval in the United States for children with achondroplasia who are 5 years of age and older and confirmatory study commitments are ongoing. Approval was based on a 1.57cm/year mean annual height velocity improvement versus placebo. In 2022, BioMarin announced positive Phase 2 results for vosoritide in infants and young children up to five years of age with achondroplasia and, in January 2023, submitted a marketing application for this indication to EU regulators. In 2023, BridgeBio announced preliminary data for Cohort 5 of the infigratinib PROPEL study (NCT04265651) demonstrating that 10 evaluable children dosed with 0.25mg/kg daily demonstrated a mean annual height velocity of 6.77cm/year and an improvement of 3.03cm/year over baseline growth velocity. In 2022 Ascendis also announced positive Phase 2 data for once-weekly TransCon CNP, a prodrug that slowly releases CNP (NCT04085523). TransCon CNP demonstrated a growth velocity improvement over placebo but Ascendis did not disclose an improvement over baseline growth velocity.

Several multi-kinase inhibitors have been approved for the treatment of HCC, but there are currently no approved FGFR4-specific inhibitors approved. There are a number of FGFR4 clinical stage programs, with most of the development focused in China. CStone Pharmaceuticals and Blueprint Medicine completed a Phase 1/2 study of BLU-554 (fisogatinib) in HCC in combination with a checkpoint inhibitor (NCT04194801). H3 Biomedicines has recruited a Phase 1/2 study of H3B-6527 in HCC (NCT02834780), but no further details are publicly available. Novartis completed a Phase 1/2 study of FGF401 alone and in combination with a checkpoint inhibitor in HCC (NCT02325739), and a similar study with FGF401 is now being conducted by Everest Medicines in combination with pembrolizumab in China.

There are two approved RET inhibitors, Lilly's Loxo Oncology's Retevmo (selpercatinib) and Blueprint Medicines' Gavreto (pralsetinib), both of which are approved for RET-positive NSCLC, PTC, and MTC. Both are conducting confirmatory Phase 3 studies in NSCLC (NCT03473756, NCT04222972) and in MTC (NCT04211337, NCT04760288). In 2022, Selpercatinib additionally achieved accelerated approval for treatment of adult patients with locally advanced or metastatic solid tumors with a *RET* gene fusion that have progressed on or following prior systemic treatment. Prior to acquisition by Bristol Myers Squibb in 2022, Turning Point Therapeutics was developing their RET candidate TPX-0046 in a Phase 1 study (NCT04161391) with stated plans to expand their study to NSCLC, MTC, and tumor agnostic populations. Boston Pharmaceuticals is developing their RET candidate zeteletinib (BOS172738) in a Phase 1 study (NCT03780517) as is Helsinn and Taiho Oncology for their partnered RET inhibitor TAS0953/HM06 (NCT04683250).

Intellectual Property

We strive to protect the intellectual property and proprietary technology that we consider important to our business through a variety of methods, including seeking and maintaining patents intended to cover our product candidates and compositions, their methods of use and processes for their manufacture, and any other inventions that are important to our business. We rely on know-how and continuing technological innovation to develop and maintain our proprietary position. We also rely on trade secrets and know-how that may be important to the development of our business. We seek to obtain domestic and international patent protection and endeavor to promptly file patent applications for new commercially valuable inventions to expand our intellectual property portfolio.

We are building a patent portfolio and have substantial confidential know-how relating to our product candidates and SNÅP platform. As of March 15, 2023, our intellectual property portfolio consisted of eight pending U.S. provisional applications, two pending U.S. nonprovisional applications, one pending European application, two Taiwanese pending applications, and three patent applications pursuant to the Patent Cooperation Treaty (PCT) all of which are solely owned by us. At this time, we do not own any issued patents in the U.S, and we do not license

any material patent rights from any third party. Collectively, our patent rights relate to various aspects of our product candidates.

We continually assess and refine our intellectual property strategy as we develop new product candidates and improvements to our SNÅP platform. To that end, we are prepared to file additional patent applications in any appropriate fields if our intellectual property strategy requires such filings, or where we seek to adapt to competition or seize business opportunities. Further, we are prepared to file patent applications, as we consider appropriate under the circumstances, relating to the new technologies that we develop.

We cannot be sure that patents will be granted with respect to any of our pending patent applications or with respect to any patent applications we may own or license in the future, nor can we be sure that any patents we may own or license in the future will be useful in protecting our technology. Please see the section entitled "Risk Factors—Risks Related to Our Intellectual Property" for additional information on the risks associated with our intellectual property strategy and portfolio.

Intellectual Property Relating to Our FGFR3 Program

With regard to our FGFR3 product candidates, as of March 15, 2023, we owned three pending U.S. provisional applications, one pending U.S. nonprovisional application, one pending PCT patent application and one Taiwanese pending application. These patent rights relate to the FGFR3 product candidates' compositions of matter, formulations containing them, methods of manufacturing, and methods of treating diseases, using our FGFR3 product candidates. Specifically, we have one PCT patent application and one Taiwanese pending application directed to the composition matter of our leading candidate in the FGFR3 program. We expect any patents issued from these applications to expire between 2040 or 2043 without accounting for any patent term adjustment or extension that may be available.

Intellectual Property Relating to Our FGFR2 Program

With regard to our FGFR2 program, as of March 15, 2023, we owned one pending U.S. nonprovisional application, one pending European application, one pending PCT patent application and one Taiwanese pending application. These patent rights relate to the FGFR2 program's compositions of matter, formulations containing them, methods of manufacturing, and methods of treating diseases. Specifically, we have one PCT patent application directed to the composition matter of our leading candidate in the FGFR2 program. We expect any patents issued from these applications to expire between 2040 and 2042 without accounting for any patent term extension that may be available.

Intellectual Property Relating to Other Programs

With regard to our other programs, including the FGFR4 program, as of March 15, 2023, we owned five pending U.S. provisional patent applications and one pending PCT patent application. These patent rights relate to these other programs' compositions of matter, formulations containing them, methods of manufacturing, and methods of treating diseases. We expect any patent issued from this application to expire between 2042 and 2043 without accounting for any patent term extension that may be available.

Scope and Duration of Intellectual Property Protection

The term of individual patents depends upon the laws of the countries in which they are obtained. In most countries in which we file, the patent term is 20 years from the earliest date of filing of a non-provisional patent application. However, the term of United States patents may be extended for delays incurred due to compliance with the FDA requirements or by delays encountered during prosecution that are caused by the USPTO. For example, for drugs that are regulated by the FDA under the Hatch-Waxman Act, the FDA is permitted to extend the term of a patent that covers such drug for up to five years beyond the normal expiration date of the patent, provided that the extended patent term may not exceed fourteen years after the date of approval of the marketing application. In the future, if and when our product candidates receive FDA approval, we expect to apply for patent term extensions on any issued U.S. patents covering those product candidates. We intend to seek patent term

extensions to any of our issued patents in jurisdictions where these are available; however, there is no guarantee that the applicable authorities, including the USPTO and FDA, will agree with our assessment of whether such extensions should be granted, and even if granted, the length of such extensions. If patents are issued on our pending patent applications, the resulting patents are expected to expire on dates ranging from 2040 to 2043, unless we receive patent term extension or patent term adjustment, or both.

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

The patent positions of companies like ours are generally uncertain and involve complex legal and factual questions. No consistent policy regarding the scope of claims allowable in patents in the field of oncology therapy has emerged in the United States. The patent situation outside of the United States is even more uncertain. Changes in the patent laws and rules, either by legislation, judicial decisions, or regulatory interpretation in the United States and other countries may diminish our ability to protect our inventions and enforce our intellectual property rights, and more generally could affect the value of our intellectual property. In particular, our ability to stop third parties from making, using, selling, offering to sell, importing or otherwise commercializing any of our patented inventions, either directly or indirectly, will depend in part on our success in obtaining, defending and enforcing patent claims that cover our technology, inventions, and improvements. With respect to both licensed and company-owned intellectual property, we cannot be sure that patents will be granted with respect to any of our pending patent applications or with respect to any patent applications filed by us in the future, nor can we be sure that any of our patents that may be granted to us in the future will be commercially useful in protecting our product candidates and the methods used to manufacture them. Moreover, those patents that may issue in the future may not guarantee us the right to practice our technology in relation to the commercialization of our product candidates.

The area of patent and other intellectual property rights in biotechnology is an evolving one with many risks and uncertainties, and third parties may have blocking patents that could be used to prevent us from commercializing our product candidates and practicing our proprietary technology. Our patents that may issue in the future may be challenged, narrowed, circumvented or invalidated, which could limit our ability to stop competitors from marketing related product candidates or limit the length of the term of patent protection that we may have for our product candidates. In addition, the rights granted under any issued patents may not provide us with protection or competitive advantages against competitors with similar technology. Furthermore, our competitors may independently develop similar technologies. For these and other reasons, we may have competition for our product candidates. Moreover, because of the extensive time required for development, testing and regulatory review of a potential product, it is possible that before any product candidate can be commercialized, any related patent may expire or remain in force for only a short period following commercialization, thereby reducing any protection afforded by the patent. For this and other risks related to our proprietary technology, inventions, improvements, SNÅP platform and product candidates, please see the section entitled “Risk Factors—Risks Related to Our Intellectual Property.”

We intend to file applications for trademark registrations in connection with our product candidates in various jurisdictions, including the United States. We have filed for trademark protection of the TYRA and TYRA BIOSCIENCES marks with the United States Patent and Trademark Office and certain foreign patent and trademark organizations.

We also rely on trade secret protection for our confidential and proprietary information. Although we take steps to protect our confidential and proprietary information as trade secrets, including through contractual means with our employees, consultants, outside scientific collaborators, sponsored researchers and other advisors, third parties may independently develop substantially equivalent proprietary information and techniques or otherwise gain access to our trade secrets or disclose our technology. Thus, we may not be able to meaningfully protect our trade secrets. It is our policy to require our employees, consultants, outside scientific collaborators, sponsored researchers and other advisors to execute confidentiality agreements under the commencement of employment or consulting relationships with us. These agreements provide that all confidential information concerning our business or financial affairs developed or made known to the individual during the individual’s

relationship with us is to be kept confidential and not disclosed to third parties except in specific circumstances. In the case of employees, the agreements provide that all inventions conceived by the individual, and which are related to our current or planned business or research and development or made during normal working hours, on our premises or using our equipment or proprietary information, are our exclusive property. In many cases our confidentiality and other agreements with consultants, outside scientific collaborators, sponsored researchers and other advisors require them to assign or grant us licenses to inventions they invent as a result of the work or services they render under such agreements or grant us an option to negotiate a license to use such inventions. Despite these efforts, we cannot provide any assurances that all such agreements have been duly executed, and any of these parties may breach the agreements and disclose our proprietary information, and we may not be able to obtain adequate remedies for such breaches.

We also seek to preserve the integrity and confidentiality of our proprietary technology and processes by maintaining physical security of our premises and physical and electronic security of our information technology systems. Although we have confidence in these individuals, organizations and systems, agreements or security measures may be breached, and we may not have adequate remedies for any breach. To the extent that our employees, contractors, consultants, collaborators and advisors use intellectual property owned by others in their work for us, disputes may arise as to the rights in relation to the resulting know-how or inventions. For more information, please see the section entitled “Risk Factors—Risks Related to Our Intellectual Property.”

Commercialization

We intend to retain significant development and commercial rights to our product candidates and, if marketing approval is obtained, to commercialize our product candidates on our own, or potentially with a partner, in the United States and other regions. We currently have no sales, marketing or commercial product distribution capabilities. We intend to build the necessary infrastructure and capabilities over time for the United States, and potentially other regions, following further advancement of our product candidates. Clinical data, the size of the addressable patient population, the size of the commercial infrastructure and manufacturing needs may all influence or alter our commercialization plans.

Manufacturing

We do not have any manufacturing facilities or personnel. We currently rely, and expect to continue to rely, on third parties for the manufacture of our product candidates undergoing preclinical testing, as well as for subsequent clinical testing and commercial manufacture if our product candidates receive marketing approval. We believe this strategy allows us to focus our expertise and resources on the development of our product candidates by eliminating the need for us to invest in our own manufacturing facilities, equipment and personnel.

We plan to put agreements in place with contract manufacturing organizations for the necessary quantities of active pharmaceutical ingredients (API) and drug product for each of our product candidates, on a project-by-project basis, based on our development needs.

As we advance our product candidates through development, we will explore adding backup suppliers for the API and drug product for each of our product candidates to protect against any potential supply disruptions.

Government Regulation

Government authorities in the United States, at the federal, state and local level, and other countries extensively regulate, among other things, the research, development, testing, manufacture, quality control, approval, labeling, packaging, storage, record-keeping, promotion, advertising, distribution, marketing and export and import of drug products. A new drug must be approved by the FDA through the New Drug Application (NDA) process before it may be legally marketed in the United States. We, along with any third-party contractors, will be required to navigate the various preclinical, clinical and commercial approval requirements of the governing regulatory agencies of the countries in which we wish to conduct studies or seek approval of our products and product candidates. The process of obtaining regulatory approvals and the subsequent compliance with applicable federal, state, local and foreign statutes and regulations require the expenditure of substantial time and financial resources.

U.S. Drug Development Process

In the United States, the FDA regulates drugs under the federal Food, Drug, and Cosmetic Act (the FDCA) and its implementing regulations. The process of obtaining regulatory approvals and the subsequent compliance with appropriate federal, state, local and foreign statutes and regulations require the expenditure of substantial time and financial resources. The process required by the FDA before a drug may be marketed in the United States generally involves the following:

- completion of preclinical laboratory tests, animal studies and formulation studies in accordance with FDA's GLP requirements and other applicable regulations;
- submission to the FDA of an IND, which must become effective before human clinical trials may begin;
- approval by an independent Institutional Review Board (IRB) or ethics committee at each clinical site before each trial may be initiated;
- performance of adequate and well-controlled human clinical trials in accordance with good clinical practices (GCPs) to establish the safety and efficacy of the proposed drug for its intended use;
- preparation of and submission to the FDA of an NDA after completion of all pivotal trials;
- a determination by the FDA within 60 days of its receipt of an NDA to file the application for review;
- satisfactory completion of an FDA advisory committee review, if applicable;
- satisfactory completion of an FDA inspection of the manufacturing facility or facilities at which the drug is produced to assess compliance with current Good Manufacturing Practice (cGMP) or similar foreign requirements to assure that the facilities, methods and controls are adequate to preserve the drug's identity, strength, quality and purity; and
- FDA review and approval of the NDA to permit commercial marketing of the product for particular indications for use in the United States.

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

Clinical trials involve the administration of the investigational product to human subjects under the supervision of qualified investigators in accordance with GCPs, which include the requirement that all research subjects provide their informed consent for their participation in any clinical study. Clinical trials are conducted under protocols detailing, among other things, the objectives of the study, the parameters to be used in monitoring safety and the effectiveness criteria to be evaluated. A separate submission to the existing IND must be made for each successive clinical trial conducted during product development and for any subsequent protocol amendments. While the IND is active, progress reports summarizing the results of the clinical trials and nonclinical studies performed since the last progress report, among other things, must be submitted at least annually to the FDA, and

written IND safety reports must be submitted to the FDA and investigators for serious and unexpected suspected adverse events, findings from other studies suggesting a significant risk to humans exposed to the same or similar drugs, findings from animal or in vitro testing suggesting a significant risk to humans, and any clinically important increased incidence of a serious suspected adverse reaction compared to that listed in the protocol or investigator brochure.

Furthermore, an independent IRB for each site proposing to conduct the clinical trial must review and approve the plan for any clinical trial and its informed consent form before the clinical trial begins at that site and must monitor the study until completed. Some studies also include oversight by an independent group of qualified experts organized by the clinical study sponsor, known as a data safety monitoring board, which provides authorization for whether or not a study may move forward at designated check points based on access to certain data from the study and may halt the clinical trial if it determines that there is an unacceptable safety risk for subjects or other grounds, such as no demonstration of efficacy. Depending on its charter, this group may determine whether a trial may move forward at designated check points based on access to certain data from the trial. The FDA or the sponsor may suspend a clinical trial at any time on various grounds, including a finding that the research subjects or patients are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution if the clinical trial is not being conducted in accordance with the IRB's requirements or if the drug has been associated with unexpected serious harm to patients. There are also requirements governing the reporting of ongoing clinical studies and clinical study results to public registries.

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

- Phase 1: The product candidate is initially introduced into healthy human subjects or patients with the target disease or condition. These studies are designed to test the safety, dosage tolerance, absorption, metabolism and distribution of the investigational product in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness.

- Phase 2: The product candidate is administered to a limited patient population with a specified disease or condition to evaluate the preliminary efficacy, optimal dosages and dosing schedule and to identify possible adverse side effects and safety risks.

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

In some cases, the FDA may require, or sponsors may voluntarily pursue, additional clinical trials after a product is approved to gain more information about the product. These so-called Phase 4 studies, may be conducted after initial marketing approval, and may be used to gain additional experience from the treatment of patients in the intended therapeutic indication. In certain instances, the FDA may mandate the performance of Phase 4 clinical trials as a condition of approval of an NDA.

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

Concurrent with clinical trials, companies usually complete additional animal studies and must also develop additional information about the chemistry and physical characteristics of the drug and finalize a process for manufacturing the product in commercial quantities in accordance with cGMP or similar foreign requirements. The manufacturing process must be capable of consistently producing quality batches of the product candidate and,

among other things, the manufacturer must develop methods for testing the identity, strength, quality and purity of the final drug. In addition, appropriate packaging must be selected and tested, and stability studies must be conducted to demonstrate that the product candidate does not undergo unacceptable deterioration over its shelf life.

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

U.S. Review and Approval Process

Assuming successful completion of all required testing in accordance with all applicable regulatory requirements, the results of product development, preclinical and other non-clinical studies and clinical trials, along with descriptions of the manufacturing process, analytical tests conducted on the chemistry of the drug, proposed labeling and other relevant information are submitted to the FDA as part of an NDA requesting approval to market the product. Data can come from company-sponsored clinical studies intended to test the safety and effectiveness of a use of the product, or from a number of alternative sources, including studies initiated by independent investigators. The submission of an NDA is subject to the payment of substantial user fees; a waiver of such fees may be obtained under certain limited circumstances. Additionally, no user fees are assessed on NDAs for products designated as orphan drugs, unless the product also includes a non-orphan indication.

The FDA conducts a preliminary review of all NDAs within the first 60 days after submission, before accepting them for filing, to determine whether they are sufficiently complete to permit substantive review The FDA may request additional information rather than accept an NDA for filing. In this event, the NDA must be resubmitted with the additional information. The resubmitted application also is subject to review before the FDA accepts it for filing. Once filed, the FDA reviews an NDA to determine, among other things, whether a product is safe and effective for its intended use and whether its manufacturing is cGMP-compliant to assure and preserve the product's identity, strength, quality and purity. Under the Prescription Drug User Fee Act guidelines that are currently in effect, the FDA has a goal of ten months from the filing date to complete a standard review of an NDA for a drug that is a new molecular entity. This review typically takes twelve months from the date the NDA is submitted to the FDA because the FDA has approximately two months to make a "filing" decision after it the application is submitted.

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

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

After the FDA evaluates an NDA and conducts any necessary inspections of manufacturing facilities where the investigational product and/or its drug substance will be produced, the FDA may issue an approval letter or a Complete Response Letter (CRL). An approval letter authorizes commercial marketing of the product with specific prescribing information for specific indications. A CRL indicates that the review cycle of the application is complete, and the application will not be approved in its present form. A CRL usually describes all of the deficiencies that the FDA has identified and may require additional clinical data, such as an additional pivotal Phase 3 clinical trial or other significant and time-consuming requirements related to clinical trials, nonclinical studies or manufacturing. When the FDA determines that the data supporting the application are inadequate to support

approval, the FDA may issue the CRL without first conducting required inspections and/or reviewing proposed labeling. In issuing the CRL, the FDA may recommend actions that the applicant might take to place the NDA in condition for approval, including requests for additional information or clarification. If a CRL is issued, the sponsor must resubmit the NDA, addressing all of the deficiencies identified in the letter, or withdraw the application. Even if such data and information are submitted, the FDA may decide that the NDA does not satisfy the criteria for approval. The FDA may delay or refuse approval of an NDA if applicable regulatory criteria are not satisfied, require additional testing or information and/or require post-marketing testing and surveillance to monitor safety or efficacy of a product.

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

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

Expedited Development and Review Programs

The FDA offers a number of expedited development and review programs for qualifying product candidates. For example, the Fast Track program is intended to expedite or facilitate the process for reviewing new product candidates that are intended to treat a serious or life-threatening disease or condition and demonstrate the potential to address unmet medical needs for the disease or condition. Fast Track designation applies to the combination of the product candidate and the specific indication for which it is being studied. The sponsor of a Fast Track product candidate has opportunities for more frequent interactions with the applicable FDA review team during product development and, once an NDA is submitted, the application may be eligible for priority review. An NDA for a Fast Track product candidate may also be eligible for rolling review, where the FDA may consider for review sections of the NDA on a rolling basis before the complete application is submitted, if the sponsor provides a schedule for the submission of the sections of the NDA, the FDA agrees to accept sections of the NDA and determines that the schedule is acceptable, and the sponsor pays any required user fees upon submission of the first section of the NDA.

A product candidate intended to treat a serious or life-threatening disease or condition may also be eligible for Breakthrough Therapy designation to expedite its development and review. A product candidate can receive Breakthrough Therapy designation if preliminary clinical evidence indicates that the product candidate, alone or in combination with one or more other drugs or biologics, may demonstrate substantial improvement over

existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. The designation includes all of the Fast Track program features, as well as more intensive FDA interaction and guidance beginning as early as Phase 1 and an organizational commitment to expedite the development and review of the product candidate, including involvement of senior managers.

Any marketing application for a drug submitted to the FDA for approval, including a product candidate with a Fast Track designation and/or Breakthrough Therapy designation, may be eligible for other types of FDA programs intended to expedite the FDA review and approval process, such as priority review and accelerated approval. An NDA is eligible for priority review if the product candidate is designed to treat a serious or life-threatening disease or condition, and if approved, would provide a significant improvement in safety or effectiveness compared to available alternatives for such disease or condition. For new-molecular-entity NDAs, priority review designation means the FDA's goal is to take action on the marketing application within six months of the 60-day filing date.

Additionally, product candidates studied for their safety and effectiveness in treating serious or life-threatening diseases or conditions may receive accelerated approval upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments. As a condition of accelerated approval, the FDA will generally require the sponsor to perform adequate and well-controlled confirmatory clinical studies to verify and describe the anticipated effect on irreversible morbidity or mortality or other clinical benefit. Products receiving accelerated approval may be subject to expedited withdrawal procedures if the sponsor fails to conduct the required confirmatory studies in a timely manner or if such studies fail to verify the predicted clinical benefit. In addition, the FDA currently requires as a condition for accelerated approval pre-approval of promotional materials, which could adversely impact the timing of the commercial launch of the product.

Fast Track designation, Breakthrough Therapy designation, priority review, and accelerated approval do not change the standards for approval, but may expedite the development or approval process. Even if a product candidate qualifies for one or more of these programs, the FDA may later decide that the product no longer meets the conditions for qualification or decide that the time period for FDA review or approval will not be shortened.

Orphan Drug Designation and Exclusivity

Under the Orphan Drug Act, the FDA may grant orphan designation to a drug intended to treat a rare disease or condition, defined as a disease or condition with a patient population of fewer than 200,000 individuals in the United States, or a patient population greater than 200,000 individuals in the United States and when there is no reasonable expectation that the cost of developing and making available the drug in the United States will be recovered from sales in the United States for that drug. Orphan drug designation must be requested before submitting an NDA. After the FDA grants orphan drug designation, the generic identity of the therapeutic agent and its potential orphan use are disclosed publicly by the FDA.

If a product that has orphan drug designation subsequently receives the first FDA approval for the drug and disease or condition for which it has such designation, the product is entitled to orphan product exclusivity, which means that the FDA may not approve any other applications, to market the same drug for the same disease or condition for seven years, except in limited circumstances, such as a showing of clinical superiority to the product with orphan drug exclusivity or if the FDA finds that the holder of the orphan drug exclusivity has not shown that it can assure the availability of sufficient quantities of the orphan drug to meet the needs of patients with the disease or condition for which the drug was designated. Orphan drug exclusivity does not prevent the FDA from approving a different drug for the same disease or condition, or the same drug for a different disease or condition. Among the other benefits of orphan drug designation are tax credits for certain research and a waiver of the NDA application user fee.

A designated orphan drug may not receive orphan drug exclusivity if it is approved for a use that is broader than the disease or condition for which it received orphan designation. In addition, orphan drug exclusive marketing rights in the United States may be lost if the FDA later determines that the request for designation was

materially defective or, as noted above, if a second applicant demonstrates that its product is clinically superior to the approved product with orphan exclusivity or the manufacturer of the approved product is unable to assure sufficient quantities of the product to meet the needs of patients with the rare disease or condition.

Post-approval Requirements

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

The FDA may withdraw approval if compliance with regulatory requirements and standards is not maintained or if problems occur after the product reaches the market. Later discovery of previously unknown problems with a product, including adverse events of unanticipated severity or frequency, or with manufacturing processes, or failure to comply with regulatory requirements, may result in revisions to the approved labeling to add new safety information; imposition of post-market studies or clinical studies to assess new safety risks; or imposition of distribution restrictions or other restrictions under a REMS program. Other potential consequences include, among other things:

- restrictions on the marketing or manufacturing of the product, complete withdrawal of the product from the market or product recalls;
- fines, warning letters, or untitled letters;
- clinical holds on clinical studies;
- refusal of the FDA to approve pending applications or supplements to approved applications, or suspension or revocation of product approvals;
- product seizure or detention, or refusal to permit the import or export of products;
- consent decrees, corporate integrity agreements, debarment or exclusion from federal healthcare programs;
- mandated modification of promotional materials and labeling and the issuance of corrective information;
- the issuance of safety alerts, Dear Healthcare Provider letters, press releases and other communications containing warnings or other safety information about the product; or
- injunctions or the imposition of civil or criminal penalties.

The FDA closely regulates the marketing, labeling, advertising and promotion of drug products. A company can make only those claims relating to safety and efficacy, purity and potency that are approved by the FDA and in accordance with the provisions of the approved label. The FDA and other agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses. Failure to comply with these requirements can result in, among other things, adverse publicity, warning letters, corrective advertising and potential civil and

criminal penalties. Physicians may prescribe, in their independent professional medical judgment, legally available products for uses that are not described in the product's labeling and that differ from those tested by us and approved by the FDA. Physicians may believe that such off-label uses are the best treatment for many patients in varied circumstances. The FDA does not regulate the behavior of physicians in their choice of treatments. The FDA does, however, restrict manufacturer's communications on the subject of off-label use of their products. However, companies may share truthful and not misleading information that is otherwise consistent with a product's FDA-approved labelling.

Marketing Exclusivity

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

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

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

FDA Regulation of Companion Diagnostics

If safe and effective use of a drug depends on an in vitro diagnostic, then the FDA may require approval or clearance of that diagnostic, known as a companion diagnostic, at the same time that the FDA approves the therapeutic product. In August 2014, the FDA issued final guidance clarifying the requirements that will apply to approval of therapeutic products and in vitro companion diagnostics. According to the guidance, if FDA determines that a companion diagnostic device is essential to the safe and effective use of a novel therapeutic product or indication, FDA may will not approve the drug or new indication if the companion diagnostic device is not also approved or cleared for that indication. Approval or clearance of the companion diagnostic device will ensure that the device has been adequately evaluated and has adequate performance characteristics in the intended population. The review of in vitro companion diagnostics in conjunction with the review of our product candidates will, therefore, likely involve coordination of review by the FDA's Center for Drug Evaluation and Research and the FDA's Center for Devices and Radiological Health Office of In Vitro Diagnostics and Radiological Health.

Under the FDCA, in vitro diagnostics, including companion diagnostics, are regulated as medical devices. In the United States, the FDCA and its implementing regulations, and other federal and state statutes and regulations govern, among other things, medical device design and development, preclinical and clinical testing,

premarket clearance or approval, registration and listing, manufacturing, labeling, storage, advertising and promotion, sales and distribution, export and import, and post-market surveillance.

Unless an exemption applies, each medical device commercially distributed in the United States generally requires either FDA clearance of a 510(k) premarket notification, or approval of a premarket approval (PMA) application. Under the FDCA, medical devices are classified into one of three classes—Class I, Class II or Class III—depending on the degree of risk associated with each medical device and the extent of manufacturer and regulatory control needed to ensure its safety and effectiveness. While most Class I devices—devices that generally pose a low risk to users—are exempt from the 510(k) premarket notification requirement, manufacturers of most Class II devices are required to submit to the FDA a premarket notification under Section 510(k) of the FDCA requesting permission to commercially distribute the device. The FDA's permission to commercially distribute a device subject to a 510(k) premarket notification is generally known as 510(k) clearance. Devices deemed by the FDA to pose the greatest risks, or devices that have a new intended use, or use advanced technology that is not substantially equivalent to that of a legally marketed device, are automatically placed in Class III, requiring approval of a PMA unless down-classified in accordance with the "de novo" process, which is a route to market for novel medical devices that are low to moderate risk and are not substantially equivalent to a predicate device.

To obtain 510(k) clearance, a manufacturer must submit to the FDA a premarket notification demonstrating that the proposed device is "substantially equivalent" to a predicate device already on the market. A predicate device is a legally marketed device that is not subject to premarket approval, i.e., a device that was legally marketed prior to May 28, 1976 (pre-amendments device) and for which a PMA is not required, a device that has been reclassified from Class III to Class II or I, or a device that was found substantially equivalent through the 510(k) process. If the FDA agrees that the device is substantially equivalent to a predicate device currently on the market, it will grant 510(k) clearance to commercially market the device. If the FDA determines that the device is "not substantially equivalent" to a previously cleared device, the device is automatically designated as a Class III device. The device sponsor must then fulfill more rigorous PMA requirements or request down-classification of the device through the "de novo" process.

The PMA process is more demanding than the 510(k) premarket notification process, and can take several years or longer. It involves a rigorous premarket review during which the applicant must prepare and provide the FDA with reasonable assurance of the device's safety and effectiveness and information about the device and its components regarding, among other things, device design, manufacturing and labeling. PMA applications are subject to an application fee. In addition, PMAs for certain devices must generally include the results from extensive preclinical and adequate and well-controlled clinical trials to establish the safety and effectiveness of the device for each indication for which FDA approval is sought. As part of the PMA review, the FDA will typically inspect the manufacturer's facilities for compliance with the QSR, which imposes elaborate testing, control, documentation and other quality assurance requirements.

If the FDA's evaluation of the PMA application is favorable, the FDA typically issues an approvable letter requiring the applicant's agreement to specific conditions, such as changes in labeling, or specific additional information, such as submission of final labeling, in order to secure final approval of the PMA. If the FDA's evaluation of the PMA or manufacturing facilities is not favorable, the FDA will deny approval of the PMA or issue a not approvable letter. A not approvable letter will outline the deficiencies in the application and, where practical, will identify what is necessary to make the PMA approvable. The FDA may also determine that additional clinical trials are necessary, in which case the PMA approval may be delayed for several months or years while the trials are conducted and then the data submitted in an amendment to the PMA. If the FDA concludes that the applicable criteria have been met, the FDA will issue a PMA for the approved indications, which can be more limited than those originally sought by the applicant. The PMA can include post-approval conditions that the FDA believes necessary to ensure the safety and effectiveness of the device, including, among other things, restrictions on labeling, promotion, sale and distribution. Once granted, PMA approval may be withdrawn by the FDA if compliance with post-approval requirements, conditions of approval or other regulatory standards are not maintained or problems are identified following initial marketing.

After a device is placed on the market, it remains subject to significant regulatory requirements. Medical devices may be marketed only for the uses and indications for which they are cleared or approved. Device manufacturers must also establish registration and device listings with the FDA. A medical device manufacturer's

manufacturing processes and those of its suppliers are required to comply with the applicable portions of the QSR, which cover the methods and documentation of the design, testing, production, processes, controls, quality assurance, labeling, packaging and shipping of medical devices. Domestic facility records and manufacturing processes are subject to periodic unscheduled inspections by the FDA. The FDA also may inspect foreign facilities that export products to the United States.

Other U.S. Healthcare Laws

Pharmaceutical companies like us are subject to additional healthcare regulation and enforcement by the federal government and by authorities in the states and foreign jurisdictions in which they conduct their business. Such regulation and enforcement may constrain the financial arrangements and relationships through which we research, develop, and ultimately, sell, market and distribute any products for which we obtain marketing approval. Such laws include, without limitation, federal and state anti-kickback, fraud and abuse, and false claims laws, such as the federal Anti-Kickback Statute and the federal civil False Claims Act, as well as federal and state transparency laws and regulations with respect to drug pricing and payments and other transfers of value made by pharmaceutical manufacturers to physicians and other health care providers, such as the federal Physician Payments Sunshine Act.

Violation of any of such laws or any other governmental regulations that apply may result in significant criminal, civil and administrative penalties including damages, fines, imprisonment, disgorgement, additional reporting requirements and oversight if we become subject to a Corporate Integrity Agreement or similar agreement to resolve allegations of non-compliance with these laws, contractual damages, reputational harm, diminished profits and future earnings, disgorgement, exclusion from participation in government healthcare programs, such as Medicare and Medicaid, and the curtailment or restructuring of our operations.

U.S. Coverage and Reimbursement

Significant uncertainty exists as to the coverage and reimbursement status of any product candidate for which we may seek regulatory approval. Sales in the United States will depend, in part, on the availability of sufficient coverage and adequate reimbursement from third-party payors, which include government health programs such as Medicare, Medicaid, TRICARE and the Veterans Administration, as well as managed care organizations and private health insurers. Prices at which we or our customers seek reimbursement for our product candidates can be subject to challenge, reduction or denial by third-party payors. For products administered under the supervision of a physician, obtaining coverage and adequate reimbursement may be particularly difficult because of the higher prices often associated with such drugs.

The process for determining whether a third-party payor will provide coverage for a product is typically separate from the process for setting the reimbursement rate that the payor will pay for the product. In the United States, there is no uniform policy among payors for coverage or reimbursement. Decisions regarding whether to cover any of a product, the extent of coverage and amount of reimbursement to be provided are made on a plan-by-plan basis. Third-party payors often rely upon Medicare coverage policy and payment limitations in setting their own coverage and reimbursement policies, but also have their own methods and approval processes. Therefore, coverage and reimbursement for products can differ significantly from payor to payor. As a result, the coverage determination process is often a time-consuming and costly process that can require manufacturers to provide scientific and clinical support for the use of a product to each payor separately, with no assurance that coverage and adequate reimbursement will be applied consistently or obtained in the first instance.

Third-party payors are increasingly challenging the price and examining the medical necessity and cost-effectiveness of medical products and services, in addition to their safety and efficacy. Adoption of price controls and cost-containment measures, and adoption of more restrictive policies in jurisdictions with existing controls and measures, could further limit sales of any product that receives approval. Third-party payors may not consider our product candidates to be medically necessary or cost-effective compared to other available therapies, or the rebate percentages required to secure favorable coverage may not yield an adequate margin over cost or may not enable us to maintain price levels sufficient to realize an appropriate return on our investment in drug development. Additionally, decreases in third-party reimbursement for any product or a decision by a third-party payor not to cover a product could reduce physician usage and patient demand for the product.

Moreover, as a condition of participating in, and having products covered under, certain federal healthcare programs, such as Medicare and Medicaid, we may become subject to federal laws and regulations that require pharmaceutical manufacturers to calculate and report certain pricing metrics to the government, including the Average Manufacturer Price (AMP) and Best Price under the Medicaid Drug Rebate Program, the Medicare Average Sales Price, the 340B Ceiling Price, and Non-Federal AMP reported to the Department of Veteran Affairs, and with respect to Medicaid, pay statutory rebates on utilization of manufacturers' products by Medicaid beneficiaries. Compliance with these laws and regulations will require significant resources and may have a material adverse effect on our revenues.

U.S. Healthcare Reform

In the United States, there has been, and continues to be, several legislative and regulatory changes and proposed changes regarding the healthcare system that could prevent or delay marketing approval of product candidates, restrict or regulate post-approval activities, and affect the profitable sale of product candidates.

Among policy makers and payors in the United States, there is significant interest in promoting changes in healthcare systems with the stated goals of containing healthcare costs, improving quality and/or expanding access. In the United States, the pharmaceutical industry has been a particular focus of these efforts and has been significantly affected by major legislative initiatives. In March 2010, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, collectively referred to as the ACA, was passed, which substantially changed the way healthcare is financed by both governmental and private insurers, and significantly affected the pharmaceutical industry. Among other changes, the ACA increased the minimum level of Medicaid rebates payable by manufacturers of brand name drugs from 15.1% to 23.1%; required collection of rebates for drugs paid by Medicaid managed care organizations; required manufacturers to participate in a coverage gap discount program, in which manufacturers must agree to offer point-of-sale discounts off negotiated prices of applicable brand drugs to eligible beneficiaries during their coverage gap period, as a condition for the manufacturer's outpatient drugs to be covered under Medicare Part D; imposed a non-deductible annual fee on pharmaceutical manufacturers or importers who sell certain "branded prescription drugs" to specified federal government programs; implemented a new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for drugs that are inhaled, infused, instilled, implanted, or injected; expanded eligibility criteria for Medicaid programs; created a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research; and established a Center for Medicare and Medicaid Innovation at the CMS to test innovative payment and service delivery models to lower Medicare and Medicaid spending, potentially including prescription drug spending.

Since its enactment, there have been judicial and political challenges to certain aspects of the ACA. On June 17, 2021, the U.S. Supreme Court dismissed the most recent judicial challenge to the ACA brought by several states without specifically ruling on the constitutionality of the ACA. Prior to the Supreme Court's decision, President Biden issued an executive order to initiate a special enrollment period from February 15, 2021 through August 15, 2021 for purposes of obtaining health insurance coverage through the ACA marketplace. The executive order also instructed certain governmental agencies to review and reconsider their existing policies and rules that limit access to healthcare, including among others, reexamining Medicaid demonstration projects and waiver programs that include work requirements, and policies that create unnecessary barriers to obtaining access to health insurance coverage through Medicaid or the ACA.

In addition, other legislative changes have been adopted since the ACA was enacted. Most recently, in March 2021, Congress enacted the American Rescue Plan Act of 2021, which, among other things, eliminated the statutory cap on drug manufacturers' Medicaid Drug Rebate Program rebate liability, effective January 1, 2024. Under current law enacted as part of the ACA, drug manufacturers' Medicaid Drug Rebate Program rebate liability is capped at 100% of the average manufacturer price for a covered outpatient drug. Other changes included aggregate reductions to Medicare payments to providers, which went into effect on April 1, 2013 and, due to subsequent legislative amendments to the statute, will remain in effect into 2032, with the exception of a temporary suspension from May 1, 2020 through March 31, 2022, unless additional Congressional action is taken. On January 2, 2013, the American Taxpayer Relief Act of 2012 was signed into law, which, among other things, reduced Medicare payments to several providers, including hospitals, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years.

Moreover, there has recently been heightened governmental scrutiny over the manner in which manufacturers set prices for their marketed products. This has resulted in several Congressional inquiries and proposed and enacted federal and state regulations designed to, among other things, bring more transparency to product pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for pharmaceutical products. On August 16, 2022, the Inflation Reduction Act of 2022 (IRA) came into law. Among other things, the IRA requires manufacturers of certain drugs to engage in price negotiations with Medicare (beginning in 2026), imposes rebates under Medicare Part B and Medicare Part D to penalize price increases that outpace inflation (first due in 2023), and replaces the Part D coverage gap discount program with a new discounting program (beginning in 2025). The IRA permits the Secretary of the Department of Health and Human Services to implement many of these provisions through guidance, as opposed to regulation, for the initial years. For that and other reasons, it is currently unclear how the IRA will be effectuated.

Individual states in the United States have also become increasingly active in implementing regulations designed to control pharmaceutical product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing. In addition, regional healthcare authorities and individual hospitals are increasingly using bidding procedures to determine which drugs and suppliers will be included in their healthcare programs. Furthermore, there has been increased interest by third party payors and governmental authorities in reference pricing systems and publication of discounts and list prices.

We expect that additional state and federal healthcare reform measures will be adopted in the future, any of which could limit the amounts that federal and state governments will pay for healthcare products and services, which could result in reduced demand for our products once approved or additional pricing pressures. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability or commercialize our product candidates.

Foreign Regulation

To market any product outside of the United States, we would need to comply with numerous and varying regulatory requirements of other countries regarding safety and efficacy and governing, among other things, clinical trials, marketing authorization, commercial sales and distribution of our products. The foreign regulatory approval process includes all of the risks associated with FDA approval set forth above, as well as additional country-specific regulation.

Whether or not we obtain FDA approval for a product, we must obtain approval of a product by the comparable regulatory authorities of foreign countries before we can commence clinical trials or marketing of the product in those countries. Approval by one regulatory authority does not ensure approval by regulatory authorities in other jurisdictions. The approval process varies from country to country, can involve additional testing beyond that required by FDA, and may be longer or shorter than that required for FDA approval. The requirements governing the conduct of clinical trials, product licensing, pricing, promotion, and reimbursement vary greatly from country to country.

Non-clinical Studies and Clinical Trials in the EU

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

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

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

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

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

The CTR foresees a three-year transition period. The extent to which ongoing and new clinical trials will be governed by the CTR varies. Clinical trials for which an application was submitted (i) prior to January 31, 2022 under the Clinical Trials Directive, or (ii) between January 31, 2022 and January 31, 2023 and for which the sponsor has opted for the application of the EU Clinical Trials Directive remain governed by said Directive until January 31, 2025. After this date, all clinical trials (including those which are ongoing) will become subject to the provisions of the CTR.

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

Marketing Authorization in the EU

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

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

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

Under the centralized procedure the maximum timeframe for the evaluation of an MAA by the EMA is 210 days, excluding clock stops. Under the above described procedures, in order to grant the MA, the EMA or the competent authorities of the EU member states make an assessment of the risk benefit balance of the product on the basis of scientific criteria concerning its quality, safety and efficacy. MAs have an initial duration of five years. After these five years, the authorization may be renewed on the basis of a reevaluation of the risk-benefit balance.

Data and Marketing Exclusivity in the EU

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

Orphan Medicinal Products in the EU

The criteria for designating an "orphan medicinal product" in the EU are similar in principle to those in the United States. A medicinal product can be designated as an orphan if its sponsor can establish that: (1) the product is intended for the diagnosis, prevention or treatment of a life threatening or chronically debilitating condition (2) either (a) such condition affects not more than five in 10,000 persons in the EU when the application is made, or (b) the product, without the benefits derived from the orphan status, would not generate sufficient return in the EU to justify the necessary investment; and (3) there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorized for marketing in the EU or, if such method exists, the product will be of significant benefit to those affected by that condition.

Orphan drug designation must be requested before submitting an MAA. An EU orphan medicinal product designation entitles a party to incentives such as reduction of fees or fee waivers, protocol assistance, and access to the centralized procedure. Upon grant of a MA, orphan medicinal products are entitled to ten years of market exclusivity for the approved indication, which means that the competent authorities cannot accept another MAA, or grant a MA, or accept an application to extend a MA for a similar medicinal product for the same indication for a period of ten years. The period of market exclusivity is extended by two years for orphan medicinal products that have also complied with an agreed pediatric investigation plan (PIP). No extension to any supplementary protection certificate can be granted on the basis of pediatric studies for orphan indications. Orphan medicinal product designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process.

The orphan exclusivity period may be reduced to six years if, at the end of the fifth year, it is established that the product no longer meets the criteria for which it received orphan drug destination, including where it is shown that the product is sufficiently profitable not to justify maintenance of market exclusivity or where the prevalence of

the condition has increased above the threshold. Additionally, MA may be granted to a similar product for the same indication at any time if (i) the second applicant can establish that its product, although similar, is safer, more effective or otherwise clinically superior; (ii) the applicant consents to a second orphan medicinal product application; or (iii) the applicant cannot supply enough orphan medicinal product.

Pediatric Development

In the EU, MAAs for new medicinal products have to include the results of studies conducted in the pediatric population, in compliance with a PIP agreed with the EMA's Pediatric Committee (PDCO). The PIP sets out the timing and measures proposed to generate data to support a pediatric indication of the drug for which MA is being sought. The PDCO can grant a deferral of the obligation to implement some or all of the measures of the PIP until there are sufficient data to demonstrate the efficacy and safety of the product in adults. Further, the obligation to provide pediatric clinical trial data can be waived by the PDCO when these data is not needed or appropriate because the product is likely to be ineffective or unsafe in children, the disease or condition for which the product is intended occurs only in adult populations, or when the product does not represent a significant therapeutic benefit over existing treatments for pediatric patients. Once the MA is obtained in all the EU member states and study results are included in the product information, even when negative, the product is eligible for six months' supplementary protection certificate extension (if any is in effect at the time of approval) or, in the case of orphan pharmaceutical products, a two year extension of the orphan market exclusivity is granted.

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

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

Regulation of Companion Diagnostics in the EU

In the EU, *in vitro* diagnostic medical devices (IVD MDs), were regulated by the EU Directive on *in vitro* diagnostic medical devices (Directive No. 98/79/EC, as amended) (IVDD), which regulated the placing on the market, the CE marking, the essential requirements, the conformity assessment procedures, the registration obligations for manufacturers and devices as well as the vigilance procedure. IVD MDs had to comply with the requirements provided for in the IVDD, and with further requirements implemented at national level (as the case may be).

The regulation of companion diagnostics is subject to further requirements since Regulation (EU) No 2017/746 (IVDR) became applicable on May 26, 2022 but there is a tiered system extending the grace period for many devices (depending on their risk classification) before they have to be fully compliant with the regulation. The IVDR introduced a new classification system for companion diagnostics which are now specifically defined as diagnostic tests that support the safe and effective use of a specific medicinal product, by identifying patients that are suitable or unsuitable for treatment. Companion diagnostics will have to undergo a conformity assessment by a notified body. Before it can issue an EU certificate, the notified body must seek a scientific opinion from the EMA on the suitability of the companion diagnostic to the medicinal product concerned if the medicinal product falls exclusively within the scope of the centralized procedure for the authorization of medicines, or the medicinal product is already authorized through the centralized procedure, or a MAA for the medicinal product has been submitted through the centralized procedure. For other substances, the notified body can seek the opinion from a national competent authorities or the EMA.

The aforementioned EU rules are generally applicable in the EEA.

Data Privacy & Security

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

Human Capital

As of March 20, 2023, we had 38 full-time employees, including a total of 13 employees with M.D. or Ph.D. degrees. Of these full-time employees, 28 employees are engaged in research and development.

None of our employees are represented by labor unions or covered by collective bargaining agreements. We consider our relationship with our employees to be good.

Our human capital resources objectives include, as applicable, identifying, recruiting, retaining, incentivizing and integrating our existing and additional employees. The principal purposes of our equity incentive plans are to attract, retain and motivate selected employees, consultants and directors through the granting of stock-based compensation awards. We value our employees and regularly benchmark total rewards we provide, such as short and long-term compensation, 401(k) plan participation, health, welfare and quality of life benefits, paid time off and personal leave, against our industry peers to ensure we remain competitive and attractive to potential new hires.

Available Information

Our internet address is www.tyra.bio. Our investor relations website is located at https://tyrabio.investorroom.com. We make available free of charge on our investor relations website under “SEC Filings” our annual reports on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K, our directors’ and officers’ Section 16 reports and any amendments to those reports as soon as reasonably practicable after filing or furnishing such materials to the SEC. They are also available for free on the SEC’s website at www.sec.gov.

We use our investor relations website as a means of disclosing material non-public information and for complying with our disclosure obligations under Regulation FD. Investors should monitor such website, in addition to following our press releases, SEC filings and public conference calls and webcasts. Information relating to our corporate governance is also included on our investor relations website The information in or accessible through the SEC and our website are not incorporated into, and are not considered part of, this filing.

Item 1A. Risk Factors.

You should carefully consider the following risk factors, together with the other information contained in this Annual Report, including our financial statements and the related notes and "Management's Discussion and Analysis of Financial Condition and Results of Operations," before making a decision to purchase or sell shares of our common stock. We cannot assure you that any of the events discussed in the risk factors below will not occur. These risks could have a material and adverse impact on our business, results of operations, financial condition and growth prospects. If that were to happen, the trading price of our common stock could decline. Additional risks and uncertainties not presently known to us or that we currently deem immaterial also may impair our business operations or financial condition. In this section, we first provide a summary of the principal risks and uncertainties we face and then provide a full set of risk factors and discuss them in greater detail.

Summary of Risks Related to Our Business

- We are very early in our development efforts, have a limited operating history, have not completed any clinical trials, have no products approved for commercial sale and have not generated any revenue, which may make it difficult for investors to evaluate our current business and likelihood of success and viability.

- We have incurred significant net losses in each period since our inception, and we expect to continue to incur significant net losses for the foreseeable future.

- Our ability to generate revenue and achieve profitability depends significantly on our ability to achieve our objectives relating to discovery, development and commercialization of our product candidates.

- We will require substantial additional financing to achieve our goals, and a failure to obtain this necessary capital when needed on acceptable terms, or at all, could force us to delay, limit, reduce or terminate our development programs, commercialization efforts or other operations.

- We are early in our development efforts, have only recently begun testing our lead product candidate in clinical trials, and our other development programs are in the preclinical or discovery stage. If we are unable to successfully develop, obtain marketing approval and ultimately commercialize product candidates, or experience significant delays in doing so, our business will be materially harmed.

- As an organization, we have only recently begun conducting our first clinical trial, and we have never submitted an application for marketing approval and may be unable to do so for any of our product candidates.

- Preclinical and clinical development involves a lengthy and expensive process with an uncertain outcome, and the results of preclinical studies and early clinical trials are not necessarily predictive of future results. We have only recently begun testing our lead product candidate in clinical trials and our product candidates may not have favorable results in clinical trials or receive marketing approval on a timely basis, if at all.

- If we encounter difficulties enrolling patients in our clinical trials, our clinical development activities could be delayed or otherwise adversely affected.

- Use of our product candidates could be associated with side effects, adverse events or other properties or safety risks, which could delay or preclude approval, cause us to suspend or discontinue clinical trials, abandon a product candidate, limit the commercial profile of an approved label or result in other significant negative consequences that could severely harm our business, prospects, operating results and financial condition.

- We intend to rely on third parties for the manufacture of our product candidates for preclinical and clinical development. This reliance on third parties increases the risk that we will not have sufficient quantities of our product candidates or products or such quantities at an acceptable cost, which could delay, prevent or impair our development or commercialization efforts.

- We rely on third parties to conduct some of our preclinical studies and our clinical trials. If these third parties do not successfully carry out their contractual duties, comply with applicable regulatory requirements or meet expected deadlines, our development programs and our ability to seek or obtain marketing approval for or commercialize our product candidates may be delayed.

- We face significant competition, and, if our competitors develop technologies or product candidates more rapidly than we do or their technologies are more effective, our business and our ability to develop and successfully commercialize products may be adversely affected.

- Our business is subject to risks arising from COVID-19 and other epidemic diseases.

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

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

Risks Related to Our Limited Operating History, Financial Position and Capital Requirements

We are very early in our development efforts, have limited operating history, have not completed any clinical trials, and have no products approved for commercial sale, which may make it difficult for investors to evaluate our current business and likelihood of success and viability.

Investment in drug development is a highly speculative undertaking and involves a substantial degree of risk. We are a biopharmaceutical company formed in 2018 with a limited operating history upon which you can evaluate our business and prospects. We have only recently begun testing our lead product candidate TYRA-300 in clinical trials. Our other development programs are either in preclinical development or in the drug discovery stage. To date, we have focused primarily on organizing and staffing our company, business planning, raising capital, research and development activities including development of our proprietary SNÅP platform and identifying potential product candidates, establishing our intellectual property portfolio, conducting research and preclinical studies and clinical trials, and providing general and administrative support to these operations. Our approach to the discovery and development of product candidates based on our proprietary SNÅP platform is unproven, and we do not know whether we will be able to develop any product candidates that are successful in clinical development or products of commercial value.

As an organization, we have not yet completed any clinical trials, obtained regulatory approvals, manufactured a commercial-scale product, or arranged for a third party to do so on our behalf, or conducted sales and marketing activities necessary for successful product commercialization. Consequently, any predictions made

about our future success or viability may not be as accurate as they could be if we had a history of successfully developing and commercializing biopharmaceutical products.

We have incurred significant net losses in each period since our inception, and we expect to continue to incur significant net losses for the foreseeable future.

We have incurred significant operating losses since our inception. Our net losses were $55.3 million and $26.3 million for the years ended December 31, 2022 and 2021, respectively. As of December 31, 2022, we had an accumulated deficit of $95.7 million. Substantially all of our losses have resulted from expenses incurred in connection with our research and development programs and from general and administrative costs associated with our operations. TYRA-300, TYRA-200 and any of our other product candidates will require substantial additional development time and resources before we are able to apply for, or receive, marketing approval and begin generating revenue from product sales. We expect to continue to incur losses for the foreseeable future, and we anticipate these losses will increase substantially as we continue our development of, and seek marketing approval for, and potentially commercialize any of our product candidates and as we seek to discover, develop and market additional potential product candidates.

Our ability to generate revenue and achieve profitability depends significantly on our ability to achieve our objectives relating to discovery, development and commercialization of our product candidates.

To generate revenue and achieve profitability, we must succeed in developing and eventually commercializing product candidates that generate significant revenue. This will require us to be successful in a range of challenging activities, including identifying lead product candidates, completing preclinical studies and clinical trials of our product candidates, discovering additional product candidates, obtaining marketing approval for these product candidates and manufacturing, marketing and selling any products for which we may obtain marketing approval. We are only in the preliminary stages of many of these activities. We may never succeed in these activities and, even if we succeed in commercializing one or more of our product candidates, we may never generate revenues that are significant or large enough to achieve profitability. In addition, we have not yet demonstrated an ability to successfully overcome many of the risks and uncertainties frequently encountered by companies in new and rapidly evolving fields, particularly in the biopharmaceutical industry.

Because of the numerous risks and uncertainties associated with biopharmaceutical product development, we are unable to accurately predict the timing or amount of increased expenses or when, or if, we will be able to achieve profitability. Even if we obtain marketing approval for one or more of our product candidates and achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis. Our failure to become and remain profitable may have an adverse effect on the value of our company and could impair our ability to raise capital, expand our business, maintain our research and development efforts, diversify our product candidates or even continue our operations. A decline in the value of our company could also cause you to lose all or part of your investment.

We will require substantial additional capital to achieve our goals, and a failure to obtain this necessary capital when needed on acceptable terms, or at all, could force us to delay, limit, reduce or terminate our development programs, commercialization efforts or other operations.

The development of biopharmaceutical product candidates is capital-intensive. We expect our expenses to increase in connection with our ongoing activities, particularly as we conduct our ongoing and planned clinical trials and preclinical studies for our product candidates and other development programs and seek marketing approval for our current product candidates and any future product candidates we may develop. If we obtain marketing approval for any of our product candidates, we also expect to incur significant commercialization expenses related to product manufacturing, marketing, sales and distribution. Because the outcome of any preclinical

study or clinical trial is highly uncertain, we cannot reasonably estimate the actual amounts necessary to successfully complete the development and commercialization of our product candidates. Furthermore, we expect to incur additional costs associated with operating as a public company. Accordingly, we will need to obtain substantial additional funding in connection with our continuing operations. If we are unable to raise capital when needed or on attractive terms, we could be forced to delay, reduce or eliminate our research and development programs or any future commercialization efforts.

Based upon our current operating plan, we believe that our existing cash and cash equivalents will enable us to fund our operations through at least until 2024. In particular, we expect that our existing cash and cash equivalents will allow us to complete the Phase 1 portion of our Phase 1/2 clinical trial for TYRA-300 and Phase 1 clinical development for TYRA-200. We have based these estimates on assumptions that may prove to be wrong, and we could use our capital resources sooner than we currently expect. Our operating plans and other demands on our cash resources may change as a result of many factors currently unknown to us, and we may need to seek additional funds sooner than planned, through public or private equity or debt financings or other capital sources, including potentially additional collaborations, licenses and other similar arrangements. In addition, we may seek additional capital due to favorable market conditions or liquidity or strategic considerations even if we believe we have sufficient funds for our current or future operating plans. For example, in October 2022, we entered into an ATM Sales Agreement (the Sales Agreement) with Virtu Americas LLC (the Agent), pursuant to which we may, from time to time, sell shares of our common stock having an aggregate offering price of up to $150 million in "at the market" offerings through or to the Agent, as sales agent or principal. However, there can be no assurance that the Agent will be successful in consummating future sales based on prevailing market conditions or in the quantities or at the prices that we deem appropriate. In addition, the Sales Agreement may be terminated by us or the Agent at any time upon specified notice to the other party, or by the Agent at any time in certain circumstances, including the occurrence of a material adverse change. Attempting to secure additional financing may divert our management from our day-to-day activities, which may adversely affect our ability to develop our product candidates.

Our future capital requirements will depend on many factors, including, but not limited to:

- the type, number, scope, progress, expansions, results, costs and timing of, discovery, preclinical studies and clinical trials of our product candidates which we are pursuing or may choose to pursue in the future;
- the costs and timing of manufacturing for our product candidates and commercial manufacturing if any product candidate is approved;
- the costs, timing and outcome of regulatory review of our product candidates;
- the costs of obtaining, maintaining and enforcing our patents and other intellectual property rights;
- our efforts to enhance operational, compliance, and quality systems and hire additional personnel to satisfy our obligations as a public company, including enhanced internal controls over financial reporting;
- the costs associated with hiring additional personnel and consultants as our preclinical and clinical activities increase;
- the costs and timing of establishing or securing sales and marketing capabilities if any product candidate is approved for commercial sale;
- our ability to achieve sufficient market acceptance, coverage and adequate reimbursement from third-party payors and adequate market share and revenue for any approved products;

- changes in laws or regulations applicable to our product candidates, including but not limited to clinical trial requirements for approval;

- the terms and timing of establishing and maintaining collaborations, licenses and other similar arrangements; and

- costs associated with any products or technologies that we may in-license or acquire.

Because we do not expect to generate commercial revenues, if any, from sales of products that we do not expect to be commercially available for many years, if at all, we will need to continue to rely on additional financing to achieve our business objectives. Adequate additional financing may not be available to us on acceptable terms, or at all, including as a result of financial and credit market deterioration or instability, market-wide liquidity shortages, geopolitical events or otherwise.

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

Until such time, if ever, as we can generate substantial product revenues, we expect to finance our cash needs through equity offerings, debt financings, or other capital sources, including potential collaborations, licenses and other similar arrangements. We do not have any committed external source of funds. To the extent that we raise additional capital through the sale of equity or convertible debt securities, your ownership interest will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect your rights as a common stockholder. Any future debt financing and preferred equity financing, if available, may involve, agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, selling or licensing our assets, making capital expenditures, declaring dividends or encumbering our assets to secure future indebtedness. Such restrictions could adversely impact our ability to conduct our operations and execute our business plan.

If we raise additional funds through future collaborations, licenses and other similar arrangements, we may have to relinquish valuable rights to our future revenue streams, research programs or product candidates, or grant licenses on terms that may not be favorable to us and/or that may reduce the value of our common stock. If we are unable to raise additional funds through equity or debt financings or other arrangements when needed or on terms acceptable to us, we would be required to delay, limit, reduce, or terminate our product development or future commercialization efforts or grant rights to develop and market product candidates that we would otherwise prefer to develop and market ourselves.

Our portfolio of investments or bank deposits may be subject to market, interest and credit risk that may reduce their value and adversely affect our business, results of operations and financial condition.

The value of our investments may decline due to increases in interest rates, downgrades of the bonds and other securities included in our commercial money market account portfolio and instability in the global financial markets that reduces the liquidity of securities included in our portfolio. In addition, the closure of Silicon Valley Bank (SVB) and Signature Bank and the appointment of the Federal Deposit Insurance Corporation (FDIC) as receiver created bank-specific and broader financial institution liquidity risk and concerns. Although the Department of the Treasury, the Federal Reserve, and the FDIC jointly released a statement that depositors at SVB and Signature Bank would have access to their funds, even those in excess of the standard FDIC insurance limits, under a systemic risk exception, future adverse developments with respect to specific financial institutions or the broader financial services industry may impair our ability to access capital needed to support near-term working capital needs, whether from our existing investment and deposit accounts and credit facilities or otherwise, and may lead to market-wide liquidity shortages and create additional market and economic uncertainty. Furthermore, a possible recession, rising inflation, and the ongoing COVID-19 pandemic has and may continue to adversely affect

the financial markets in some or all countries worldwide. Each of these events may cause us to record charges to reduce the carrying value of our investment portfolio or sell investments for less than our acquisition cost. Although we attempt to mitigate these risks through diversification of our investments, the value of our investments may nevertheless decline, and our ability to fund our near-term and long-term working capital needs to support our business and clinical development plans may be adversely affected. In addition, any decline in available funding or access to our cash and liquidity resources could also result in breaches of our financial and/or contractual obligations or result in violations of federal or state wage and hour laws.

Risks Related to the Discovery, Development and Marketing Approval of Our Product Candidates

We are early in our development efforts, have only recently begun clinical trials of our lead product candidate and all of our other development programs are in the preclinical or discovery stage. If we are unable to successfully develop, obtain marketing approval and ultimately commercialize product candidates, or experience significant delays in doing so, our business will be materially harmed.

We are in the early stages of our research and development efforts and all of our development programs are either in early clinical development or the preclinical or drug discovery stage. We have invested substantially all of our efforts to date in developing our proprietary SNÅP platform, developing TYRA-300 and TYRA-200, identifying other potential product candidates and conducting preclinical studies. Although we have recently advanced TYRA-300 into clinical trials in adults with advanced urothelial carcinoma and other solid tumors with FGFR3 gene alterations and recently received clearance from the U.S. Food and Drug Administration (FDA) on our Investigational New Drug application (IND) to proceed with a Phase 1 clinical study of TYRA-200, we are very early in our clinical trials of TYRA-300, have not commenced clinical study of TYRA-200 and will need to progress our other development programs through additional preclinical studies to enable us to submit INDs with the FDA and receive allowance from the FDA to proceed with initiating their clinical development, including for TYRA-300 in pediatric achondroplasia. Our ability to generate product revenues, which we do not expect will occur for many years, if ever, will depend on the successful development and eventual commercialization of our product candidates. The success of our product candidates will depend on several factors, including the following:

- successful completion of preclinical studies with favorable results, including those compliant with Good Laboratory Practice (GLP) such as toxicology studies, biodistribution studies and minimum effective dose studies in animals;
- acceptance by the FDA of INDs or of similar regulatory submissions by comparable foreign regulatory authorities for the conduct of clinical trials of our product candidates and our proposed design of future clinical trials;
- successful identification of appropriate patients eligible to enroll, and enrollment of such patients, in clinical trials and completion of clinical trials with favorable results;
- successful identification of new product candidates utilizing our SNÅP platform;
- demonstrating safety and efficacy to the satisfaction of applicable regulatory authorities;
- making arrangements with our third-party manufacturers for, or establishing, commercial manufacturing capabilities;
- receipt of marketing approvals from applicable regulatory authorities, including new drug applications (NDAs), from the FDA and maintaining such approvals;
- establishing sales, marketing and distribution capabilities and launching commercial sales of our products, if and when approved, whether alone or in collaboration with others;

- establishing and maintaining patent and trade secret protection or regulatory exclusivity for our product candidates;

- maintaining an acceptable safety profile of our products following marketing approval, including acceptable results from any post-approval studies or clinical trials agreed to by us or required by the FDA; and

- maintaining and growing an organization of people who can develop and commercialize our product candidates.

The FDA or comparable foreign regulatory authorities can refuse to accept INDs or similar regulatory submissions for many reasons, including negative or ambiguous results from our preclinical studies or disagreement with our interpretation of data from preclinical studies. If we are unable to develop, obtain marketing approval for, or, if approved, successfully commercialize our product candidates, we may not be able to generate sufficient revenue to continue our business.

As an organization, we have never completed any clinical trials or submitted an application for marketing approval, and may be unable to do so for any of our product candidates.

We are early in our development efforts for our product candidates and we will need to successfully complete IND-enabling studies, Phase 1 clinical trials and later-stage and pivotal clinical trials, in order to obtain marketing authorization from the FDA or comparable foreign regulatory authorities to market TYRA-300, TYRA-200 or any other product candidates. Carrying out clinical trials and the submission of a successful NDA is a complicated process. As an organization, we only recently commenced our SURF301 Phase 1/2 clinical trial in November 2022 and recently received clearance from the FDA on our IND to proceed with a Phase 1 clinical study of TYRA-200. Our other development programs are in the preclinical development stage. We have not previously completed any clinical trials, have limited experience as a company in preparing, submitting and prosecuting regulatory filings and have not previously submitted an NDA or other comparable foreign regulatory submission for any product candidate. If we decide to develop TYRA-300 or TYRA-200 for multiple indications, we may be required to submit multiple INDs to the FDA for these development programs and may not conduct a clinical trial in the United States for that indication until we do so. For example, we will be required to complete IND-enabling studies of TYRA-300 in pediatric achondroplasia to support an IND submission prior to commencing clinical development. In addition, we have had limited interactions with the FDA and cannot be certain how many clinical trials of TYRA-300, TYRA-200 or any other product candidates will be required or how such trials should be designed. Consequently, we may be unable to successfully and efficiently execute and complete necessary clinical trials in a way that leads to regulatory submission and approval of any of our product candidates. We may require more time and incur greater costs than our competitors and may not succeed in obtaining marketing approvals of product candidates that we develop. Failure to commence or complete, or delays in, our ongoing or planned clinical trials, could prevent us from, or delay us in submitting NDAs for, and commercializing our product candidates.

Preclinical and clinical development involves a lengthy and expensive process with an uncertain outcome, and the results of preclinical studies and early clinical trials are not necessarily predictive of future results. Our product candidates may not have favorable results in clinical trials, if any, or receive marketing approval on a timely basis, if at all.

Preclinical and clinical development is expensive and can take many years to complete, and its outcome is inherently uncertain. We cannot guarantee that any preclinical studies or clinical trials will be conducted as planned or completed on schedule, if at all, and delay or failure can occur at any time during the preclinical study or clinical trial process, including due to factors that are beyond our control. Further, we may not be able to meet expected timeframes for data readouts. Despite promising preclinical or clinical results, any biopharmaceutical company's product candidate can unexpectedly fail at any stage of preclinical or clinical development, and

regulators, such as the FDA or comparable foreign regulatory authorities, may not accept the results as demonstrating the product candidate's safety and efficacy. The historical failure rate for product candidates in our industry is high.

The results from preclinical studies or clinical trials of a product candidate may not predict the results of later clinical trials of the product candidate, and interim, topline, or preliminary results of a clinical trial are not necessarily indicative of final results. Product candidates in later stages of clinical trials may fail to show the desired safety and efficacy characteristics despite having progressed through preclinical studies and initial clinical trials. In particular, while we have conducted certain preclinical studies of TYRA-300, TYRA-200 and other potential product candidates targeting acquired resistance mutations in FGFR3, RET, and FGFR4, we do not know whether TYRA-300, TYRA-200 or the other potential product candidates will perform in current or future clinical trials as they have performed in these prior studies. The positive results we have observed for our product candidates in preclinical animal models may not be predictive of our current or future clinical trials in humans. It is not uncommon to observe results in clinical trials that are unexpected based on preclinical studies and early clinical trials, and many product candidates fail in clinical trials despite very promising early results. We have recently commenced a Phase 1/2 clinical trial evaluating TYRA-300 and recently received clearance from the FDA on our IND to proceed with a Phase 1 clinical study of TYRA-200. If unexpected observations or toxicities are observed in these trials, or in IND-enabling studies for any of our other product candidates, such results could delay and possibly prevent or limit clinical trials for our product candidates. Moreover, preclinical and clinical data may be susceptible to varying interpretations and analyses. A number of companies in the biopharmaceutical and biotechnology industries have suffered significant setbacks in clinical development even after achieving promising results in earlier studies. Such setbacks have occurred and may occur for many reasons, including, but not limited to: clinical sites and investigators may deviate from clinical trial protocols, whether due to lack of training or otherwise, and we may fail to detect any such deviations in a timely manner; patients may fail to adhere to any required clinical trial procedures, including any requirements for post-treatment follow-up; our product candidates may fail to demonstrate effectiveness or safety in certain patient subpopulations, which has not been observed in earlier trials due to limited sample size, lack of analysis or otherwise; or our clinical trials may not adequately represent the patient populations we intend to treat, whether due to limitations in our trial designs or otherwise, such as where one patient subgroup is overrepresented in the clinical trial. There can be no assurance that we will not suffer similar setbacks despite the data we observed in earlier or ongoing studies. Based upon negative or inconclusive results, we or any future collaborator may decide, or regulators may require us, to conduct additional preclinical studies or clinical trials, which would cause us to incur additional operating expenses and delays and may not be sufficient to support regulatory approval on a timely basis or at all.

For the foregoing reasons, we cannot be certain that our ongoing and planned preclinical studies and clinical trials will be successful. In addition, any safety concerns observed in any one of our clinical trials in our targeted indications could impair the development, marketing approval or commercial prospects of our product candidates in those and other indications, such as TYRA-300 for oncology and achondroplasia, which could have a material adverse effect on our business, financial condition and results of operations.

Our discovery and preclinical development activities are focused on the development of targeted therapeutics for patients with genomically defined cancers, which is a rapidly evolving area of science, and the approach we are taking to discover and develop drugs based on our SNÅP platform is novel and unproven and may never lead to approved products of commercial value.

The discovery and development of targeted therapeutics for patients with genomically defined cancers is an emerging field, and the scientific discoveries that form the basis for our efforts to discover and develop product candidates are relatively new. Although we believe, based on our preclinical work, that the genomic alterations targeted by our programs are oncogenic drivers, clinical results may not confirm this hypothesis or may only confirm it for certain alterations or certain tumor types. In addition, even if our approach is successful in showing

clinical benefit for acquired resistance mutation-driven cancers for our TYRA-300 and TYRA-200 inhibitor programs, we may never successfully identify additional oncogenic alterations for other receptor tyrosine kinases using our SNÅP platform, or succeed in identifying additional product candidates to address such alterations. Any product candidates we do discover and advance based on scientific approach may be later shown to have harmful side effects or may have other characteristics that may necessitate additional clinical testing, or make the product candidates unmarketable or unlikely to receive marketing approval. Therefore, we do not know if our approach of discovering and developing product candidates to treat patients with genomically defined cancers will be successful, and if our approach is unsuccessful, we may be forced to abandon our development efforts for a program or programs, which would have a material adverse effect on our business and could potentially cause us to cease operation.

Any difficulties or delays in the commencement or completion, or termination or suspension, of our clinical trials could result in increased costs to us, delay or limit our ability to generate revenue and adversely affect our commercial prospects.

Before we can initiate clinical trials for our product candidates, we must submit the results of preclinical studies to the FDA or comparable foreign regulatory authorities along with other information, including information about product candidate chemistry, manufacturing and controls and our proposed clinical trial protocol, as part of an IND or similar regulatory filing required for regulatory allowance before proceeding with clinical development. We will also need to complete IND-enabling studies and submit INDs for TYRA-300 in pediatric achondroplasia our other development programs prior to initiating clinical development. The FDA or comparable foreign regulatory authorities may require us to conduct additional preclinical studies for any product candidate before it allows us to initiate clinical trials under any IND or similar regulatory filing, which may lead to delays and increase the costs of our preclinical development programs. Moreover, even if these trials begin, issues may arise that could cause regulatory authorities to suspend or terminate such clinical trials. Any such delays in the commencement or completion of our ongoing or planned clinical trials for TYRA-300, TYRA-200, or any other product candidate, could significantly affect our product development timelines and development costs.

We do not know whether our planned trials will begin on time or be completed on schedule, if at all. The commencement, data readouts and completion of clinical trials can be delayed for a number of reasons, including delays related to:

- inability to generate sufficient preclinical, toxicology, or other *in vivo* or in vitro data to support the initiation or continuation of clinical trials;
- obtaining regulatory clearance to commence a trial or reaching a consensus with regulatory authorities on trial design;
- the FDA or comparable foreign regulatory authorities disagreeing as to the design or implementation of our clinical trials;
- any failure or delay in reaching an agreement with contract research organizations (CROs) and clinical trial sites, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and trial sites;
- failure to reach an agreement with diagnostic companies for the development and use of liquid biopsy companion diagnostic tests in our clinical trials;
- obtaining approval from one or more institutional review boards (IRBs);
- IRBs refusing to approve, suspending or terminating the trial at an investigational site, precluding enrollment of additional patients, or withdrawing their approval of the trial;

- changes to clinical trial protocol;
- identifying sufficient appropriately qualified investigators and other professionals to conduct the clinical trials;
- clinical sites deviating from trial protocol or dropping out of a trial;
- manufacturing sufficient quantities of product candidates for use in clinical trials;
- patients failing to enroll or remain in our trials at the rate we expect, or failing to return for post-treatment follow-up, including patients failing to remain in our trials due to movement restrictions, health reasons or otherwise resulting from the COVID-19 pandemic or other epidemic diseases;
- patients choosing an alternative treatment for the indication for which we are developing our product candidates, or participating in competing clinical trials;
- lack of adequate funding to continue the clinical trials;
- patients experiencing severe or unexpected drug-related adverse effects;
- occurrence of serious adverse events in clinical trials of the same class of agents conducted by other companies;
- selection of clinical endpoints that require prolonged periods of clinical observation or analysis of the resulting data;
- a facility manufacturing our product candidates or any of their components suspending or limiting manufacturing due to violations of cGMP, or other applicable requirements, including infections or cross-contaminations of product candidates in the manufacturing process, or the facility being subject to other enforcement by the FDA or comparable foreign regulatory authorities that result in temporary or permanent manufacturing shut downs or product supply limitations;
- any changes to our manufacturing process that may be necessary or desired;
- third-party clinical investigators losing the licenses or permits necessary to perform our clinical trials or being suspended or disqualified by the FDA or comparable foreign regulatory authorities, not performing our clinical trials on our anticipated schedule or consistent with the clinical trial protocol, GCPs, or other regulatory requirements;
- third-party contractors not performing data collection or analysis in a timely or accurate manner; or
- third-party contractors becoming debarred or suspended or otherwise penalized by the FDA or comparable foreign regulatory authorities for violations of regulatory requirements, in which case we may need to find a substitute contractor, and we may not be able to use some or all of the data produced by such contractors in support of our marketing applications.

In addition, disruptions caused by the COVID-19 pandemic or any future epidemic diseases may increase the likelihood that we encounter such difficulties or delays in initiating, enrolling, conducting or completing our planned and ongoing clinical trials. We could also encounter delays if a clinical trial is suspended or terminated by us, by the IRBs of the institutions in which our trials are being conducted, by a Data Safety Monitoring Board for our trial or by the FDA or comparable foreign regulatory authorities. These authorities may impose such a suspension or termination due to a number of factors, including failure to conduct the clinical trial in accordance with regulatory requirements or our clinical protocols and to make the appropriate required records, inspection of the clinical trial operations or trial site by the FDA or comparable foreign regulatory authorities resulting in the imposition of a clinical hold, unforeseen safety issues or adverse side effects, failure to demonstrate a benefit from

using a clinical trial drug, changes in governmental regulations or administrative actions or lack of adequate funding to continue the clinical trial. In addition, changes in regulatory requirements and policies may occur, and we may need to amend clinical trial protocols to comply with these changes. Amendments may require us to resubmit our clinical trial protocols to IRBs for reexamination, which may impact the costs, timing or successful completion of a clinical trial.

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

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

If we experience delays in the completion of, or termination of, any clinical trial of our product candidates, the commercial prospects of our product candidates will be harmed, and our ability to generate product revenues from any of these product candidates will be delayed. Moreover, any delays in completing our clinical trials will increase our costs, slow down our product candidate development and approval process and jeopardize our ability to commence product sales and generate revenues.

Our proprietary SNÅP platform is innovative and unproven, and we do not know whether we will be able to develop any product candidates that are successful in clinical development or products of commercial value.

The success of our business depends primarily upon our ability to identify, develop and commercialize products based on our proprietary SNÅP platform, which is designed to efficiently identify and selectively target vulnerabilities in the mutant proteins that commonly eliminate or reduce the effectiveness of standard-of-care therapies. We have not yet succeeded and may not succeed in demonstrating efficacy and safety for any product candidates in clinical trials or in obtaining marketing approval thereafter. TYRA-300 and TYRA-200 are in the early stages of development and we have not yet completed any clinical trials for any product candidate. Our SNÅP platform utilizes the rapid generation of precise molecular SNÅPshots to continually gain deeper insights into the structure of inhibitor binding sites and how commonly occurring resistance mutations lead to acquired drug resistance to existing therapies, which we believe aids in the prediction of amino acid residues most likely to cause resistance to specific existing therapies. This innovative process may never be successful in identifying additional product candidates with innovative structures that are able to inhibit the target while avoiding those specific residues. Further, because all of our product candidates and discovery programs are based on our SNÅP platform, adverse developments with respect to one of our programs may have a significant adverse impact on the actual or perceived likelihood of success and value of our other development programs.

In addition, the biotechnology and biopharmaceutical industries are characterized by rapidly advancing technologies. Our future success will depend in part on our ability to maintain a competitive position with our innovative approach to compound identification. If we fail to stay at the forefront of technological innovation in utilizing our SNÅP platform, we may be unable to compete effectively.

If we encounter difficulties enrolling patients in our clinical trials, our clinical development activities could be delayed or otherwise adversely affected.

We may not be able to complete clinical trials for our product candidates if we are unable to identify and enroll a sufficient number of eligible patients to participate in these trials as required by the FDA or comparable foreign regulatory authorities. Patient enrollment for our clinical trials may be affected by many factors, including:

- the size and nature of the patient population;
- the proximity of patients to clinical sites;
- the eligibility and exclusion criteria for the trial;
- the design of the clinical trial;
- the risk that enrolled patients will not complete a clinical trial;
- our ability to recruit clinical trial investigators with the appropriate competencies and experience; and
- competing clinical trials and clinicians' and patients' perceptions as to the potential advantages and risks of the product candidate being studied in relation to other available therapies, including any new products that may be approved for the indications we are investigating as well as any product candidates under development.

We will be required to identify and enroll a sufficient number of patients for each of our clinical trials. The patient populations for our product candidates are limited to those with specific target alterations and may not be completely defined but are substantially smaller than the general treated cancer population, and we will need to screen and identify these patients with targeted alterations. Successful identification of patients is dependent on several factors, including achieving certainty as to how specific alterations respond to our product candidates and the ability to identify such alterations. Furthermore, even if we are successful in identifying patients, we cannot be certain that the resulting patient populations for each mutation will be large enough to allow us to successfully obtain approval for each mutation type and commercialize our product candidates and achieve profitability. We may not be able to initiate or continue clinical trials if we are unable to locate a sufficient number of eligible patients to participate in the clinical trials required by the FDA or comparable foreign regulatory authorities. In addition, the process of finding and diagnosing patients may prove costly.

The timing of our clinical trials depends, in part, on the speed at which we can recruit patients to participate in our trials, as well as completion of required follow-up periods. The eligibility criteria of our clinical trials, once established, will further limit the pool of available trial participants. If patients are unwilling to participate in our trials for any reason, including the existence of concurrent clinical trials for similar patient populations or the availability of other therapies, or we otherwise have difficulty enrolling a sufficient number of patients, the timeline for recruiting patients, conducting clinical trials and obtaining marketing approval of our product candidates may be delayed. Additionally, because our initial clinical trials will be in patients with relapsed/refractory cancer, these patients are typically in the late stages of their disease and may experience disease progression independent from our product candidates, making them unevaluable for purposes of the clinical trial and requiring additional patient enrollment. Our inability to enroll a sufficient number of patients for any of our clinical trials would result in significant delays or may require us to abandon one or more clinical trials altogether. In addition, we expect to rely on CROs and clinical trial sites to ensure proper and timely conduct of our clinical trials and, while we intend to enter into agreements governing their services, we will have limited influence over their actual performance.

We cannot assure you that our assumptions used in determining expected clinical trial timelines are correct or that we will not experience delays in enrollment, which would result in the delay of completion of such trials beyond our expected timelines.

Use of our product candidates could be associated with side effects, adverse events or other properties or safety risks, which could delay or preclude approval, cause us to suspend or discontinue clinical trials, abandon a product candidate, limit the commercial profile of an approved label or result in other significant negative consequences that could severely harm our business, prospects, operating results and financial condition.

We have not evaluated any of our product candidates in human clinical trials. It is impossible to predict when or if any product candidates we may develop will prove safe in humans. As is the case with biopharmaceuticals generally, and treatments for cancer and rare diseases in particular, it is likely that there may be side effects and adverse events associated with the use of our product candidates. Results of our clinical trials could reveal a high and unacceptable severity and prevalence of side effects or unexpected characteristics. Undesirable side effects caused by our product candidates could cause us or regulatory authorities to interrupt, delay or halt clinical trials and could result in a more restrictive label or the delay or denial of marketing approval by the FDA or comparable foreign regulatory authorities. If adverse events or other side effects are observed in any of our clinical trials, we may have difficulty recruiting patients to our clinical trials, patients may drop out of our trials, or we may be required to abandon the trials or our development efforts of one or more product candidates altogether. Any of these occurrences may harm our business, financial condition and prospects significantly.

Moreover, if our product candidates are associated with undesirable side effects in clinical trials or have characteristics that are unexpected, we may elect to abandon their development or limit their development to more narrow uses or subpopulations in which the undesirable side effects or other characteristics are less prevalent, less severe or more acceptable from a risk-benefit perspective, which may limit the commercial expectations for the product candidate if approved. Any such undesirable side effects observed in one of our clinical trials in our targeted indications could impair the development, marketing approval or commercial prospects of our product candidates in those and other indications, such as TYRA-300 for oncology and achondroplasia. We, the FDA or other applicable regulatory authorities, or an IRB, may suspend or terminate future clinical trials of a product candidate at any time for various reasons, including a belief that subjects in such trials are being exposed to unacceptable health risks or adverse side effects. Many compounds that initially showed promise in early-stage testing have later been found to cause side effects that prevented further development of the compound. In addition, regulatory authorities may draw different conclusions or require additional testing to confirm these determinations.

It is possible that as we test our product candidates in larger, longer and more extensive clinical trials, including with different dosing regimens, or as the use of these product candidates becomes more widespread if they receive marketing approval, illnesses, injuries, discomforts and other adverse events that were observed in earlier trials, as well as conditions that did not occur or went undetected in previous trials, may be reported by patients. If such side effects become known later in development or upon approval, if any, such findings may harm our business, financial condition and prospects significantly.

Patients treated with our products, if approved, may experience previously unreported adverse reactions, and it is possible that the FDA or comparable foreign regulatory authorities may ask for additional safety data as a condition of, or in connection with, our efforts to obtain approval of our product candidates. Even if the side effects do not preclude the product candidate from obtaining or maintaining marketing approval, undesirable side effects may inhibit market acceptance of the approved product due to its tolerability versus other therapies. If safety problems occur or are identified after our products, if any, are available for commercial sale and use, we may make the decision, or be required by regulatory authorities, to amend the labeling of our product candidates, recall our product candidates or even withdraw approval for an approved product.

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

- regulatory authorities may withdraw, suspend or limit approvals of such product, or seek an injunction against its manufacture or distribution;
- we may be required to recall a product or change the way such product is administered to patients;
- regulatory authorities may require additional warnings on the label, such as a "black box" warning or a contraindication;
- we may be required to implement a Risk Evaluation and Mitigation Strategy (REMS) or create a medication guide outlining the risks of such side effects for distribution to patients;
- we may be required to change the way a product is distributed, conduct additional clinical trials or change the labeling of a product or be required to conduct additional post-marketing studies or surveillance;
- we could be sued and held liable for harm caused to patients; or
- sales of the product may decrease significantly or the product could become less competitive and our reputation may suffer.

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

We may not be able to submit future INDs to commence clinical trials on the timelines we expect, and even if we are able to, the FDA may not permit us to proceed.

We may not be able to submit additional INDs for our existing and future product candidates on the timelines we expect. For example, we may experience manufacturing delays or other delays with IND-enabling studies. Moreover, we cannot be sure that submission of an IND will result in the FDA allowing clinical trials to begin, or that, once begun, issues will not arise that suspend or terminate clinical trials. Additionally, even if the FDA agrees with the design and implementation of the clinical trials set forth in an IND, we cannot guarantee that it will not change its requirements in the future. These considerations also apply to new clinical trials we may submit as amendments to existing INDs or to a new IND. Any failure to file INDs on the timelines we expect or to obtain regulatory approvals for our planned clinical trials may prevent us from initiating or completing our clinical trials or commercializing our product candidates on a timely basis, if at all.

Our product candidates are subject to extensive regulation and compliance, which is costly and time consuming, and such regulation may cause unanticipated delays or prevent the receipt of the required approvals to commercialize our product candidates.

The clinical development, manufacturing, labeling, packaging, storage, record-keeping, advertising, promotion, import, export, marketing, distribution and adverse event reporting, including the submission of safety and other information, of our product candidates are subject to extensive regulation by the FDA in the United States and by comparable foreign regulatory authorities in foreign markets. In the United States, we are not permitted to market our product candidates until we receive marketing approval from the FDA. The process of obtaining marketing approval is expensive, often takes many years following the commencement of clinical trials and can vary substantially based upon the type, complexity and novelty of the product candidates involved, as well as the target indications and patient population. Approval policies or regulations may change, and the FDA has substantial

discretion in the drug approval process, including the ability to delay, limit or deny approval of a product candidate for many reasons. Despite the time and expense invested in clinical development of product candidates, marketing approval is never guaranteed. Neither we, nor any future collaborator, is permitted to market any of our product candidates in the United States until we receive marketing approval from the FDA.

Prior to obtaining approval to commercialize a product candidate in the United States or abroad, we or our collaborators must demonstrate with substantial evidence from adequate and well-controlled clinical trials, and to the satisfaction of the FDA or comparable foreign regulatory authorities, that such product candidates are safe and effective for their intended uses. Results from preclinical studies and clinical trials can be interpreted in different ways. Even if we believe the preclinical or clinical data for our product candidates are promising, such data may not be sufficient to support approval by the FDA or comparable foreign regulatory authorities. The FDA or comparable foreign regulatory authorities, as the case may be, may also require us to conduct additional preclinical studies or clinical trials for our product candidates either prior to or post-approval, or may object to elements of our clinical development program.

The FDA or comparable foreign regulatory authorities can delay, limit or deny approval of a product candidate for many reasons, including:

- such authorities may disagree with the design or implementation of our, or our any of our potential future collaborators' clinical trials;
- negative or ambiguous results from our clinical trials or results may not meet the level of statistical significance required by the FDA or comparable foreign regulatory authorities for marketing approval;
- serious and unexpected drug-related side effects may be experienced by participants in our clinical trials or by individuals using drugs similar to our product candidates;
- such authorities may not accept clinical data from trials which are conducted at clinical facilities or in countries where the standard of care is potentially different from that of the United States;
- we, or any of our potential future collaborators may be unable to demonstrate that a product candidate is safe and effective, and that product candidate's clinical and other benefits outweigh its safety risks;
- such authorities may disagree with our interpretation of data from preclinical studies or clinical trials;
- such authorities may not agree that the data collected from clinical trials of our product candidates are acceptable or sufficient to support the submission of an NDA or other submission or to obtain marketing approval in the United States or elsewhere, and such authorities may impose requirements for additional preclinical studies or clinical trials;
- such authorities may disagree regarding the formulation, labeling and/or the specifications of our product candidates;
- such authorities may require additional information, data, qualification, or validation of our manufacturing and testing processes as part of the chemistry, manufacturing, and controls information we submit as part of our application;
- approval may be granted only for indications that are significantly more limited than what we apply for and/or with other significant restrictions on distribution and use;

- such authorities may find deficiencies in the manufacturing processes, approval policies or facilities of our third-party manufacturers with which we or any of our current or future collaborators contract for clinical and commercial supplies;

- regulations of such authorities may significantly change in a manner rendering our or any of our potential future collaborators' clinical data insufficient for approval; or

- such authorities may not accept a submission due to, among other reasons, the content or formatting of the submission.

Any delays in the marketing approval of our product candidates may negatively impact our ability to successfully position the product candidate in the market or the product candidate may face additional competition from other products.

With respect to foreign markets, marketing approval procedures vary among countries and, in addition to the foregoing risks, may involve additional product testing, administrative review periods and agreements with pricing authorities. In addition, events raising questions about the safety of certain marketed biopharmaceuticals may result in increased cautiousness by the FDA or comparable foreign regulatory authorities in reviewing new drugs based on safety, efficacy or other regulatory considerations and may result in significant delays in obtaining marketing approvals. Any delay in obtaining, or inability to obtain, applicable marketing approvals would prevent us or any of our potential future collaborators from commercializing our product candidates.

If we are unable to successfully develop companion diagnostics for biomarkers that enable patient selection, or experience significant delays in doing so, we may not be able to commercialize the product candidate and our ability to generate revenue will be materially impaired.

A key component of our strategy includes the use of companion diagnostics to guide patient selection of our product candidates. We do not have the ability to develop such tests on our own, and so we plan to rely on third parties for the design, development and manufacture of companion diagnostic tests for any of our product candidates that may require such tests. If we enter into such collaborative agreements, we will be dependent on the sustained cooperation and effort of our future collaborators in developing and obtaining approval, certification or clearance for these companion diagnostics. To be successful in developing and commercializing product candidates in combination with these companion diagnostics, we and our future collaborators will need to address a number of scientific, technical, regulatory and logistical challenges.

According to FDA guidance, if the FDA determines that a companion diagnostic device is essential to the safe and effective use of a novel therapeutic product or indication, the FDA generally will not approve the therapeutic product or new therapeutic product indication if the companion diagnostic is not also approved or cleared at the same time the product candidate is approved. To date, the FDA has generally required premarketing approval companion diagnostic tests for cancer therapies. Various foreign regulatory authorities also regulate in vitro companion diagnostics as medical devices and, under those regulatory frameworks, will likely require the conduct of clinical trials to demonstrate the safety and effectiveness of these companion diagnostics, which we expect will require separate regulatory clearance or approval prior to commercialization.

The approval, certification or clearance of a companion diagnostic as part of the therapeutic product's labeling limits the use of the therapeutic product to only those patients who express certain biomarkers or the specific genomic alteration that the companion diagnostic was developed to detect. If the FDA or comparable foreign regulatory authorities require approval or clearance of a companion diagnostic for any of our product candidates, whether before or concurrently with marketing approval of the product candidate, we and/or our collaborators, may encounter difficulties in developing and obtaining approval, certification or clearance for these companion diagnostics. Any delay or failure by us or potential future collaborators to develop or obtain regulatory

approval or clearance of a companion diagnostic could delay or prevent approval, certification or continued marketing of our related product candidates.. Indeed, approval, certification or clearance of companion diagnostics may be subject to further legislative or regulatory reforms notably in the EU. On May 25, 2017, the new In Vitro Medical Devices Regulation (IVDR) entered into force. The IVDR repeals and replaces the EU In Vitro Diagnostic Medical Devices Directive. Unlike directives, which must be implemented into the national laws of the EU member states, regulations are directly applicable, i.e., without the need for adoption of EU member states laws implementing them, in all EU member states and are intended to eliminate current differences in the regulation of medical devices among EU member states. The IVDR, among other things, is intended to establish a uniform, transparent, predictable and sustainable regulatory framework across the EU for medical devices and ensure a high level of safety and health while supporting innovation. The IVDR became applicable on May 26, 2022 but there is a tiered system extending the grace period for many devices (depending on their risk classification) before they have to be fully compliant with the regulation.

The regulation of companion diagnostics is subject to further requirements since the IVDR became applicable as it introduced a new classification system for companion diagnostics which are now specifically defined as diagnostic tests that support the safe and effective use of a specific medicinal product, by identifying patients that are suitable or unsuitable for treatment. Companion diagnostics will have to undergo a conformity assessment by a notified body. Before it can issue an EU certificate, the notified body must seek a scientific opinion from the EMA on the suitability of the companion diagnostic to the medicinal product concerned if the medicinal product falls exclusively within the scope of the centralized procedure for the authorization of medicines, or the medicinal product is already authorized through the centralized procedure, or a marketing authorization application for the medicinal product has been submitted through the centralized procedure. For other substances, the notified body can seek the opinion from a national competent authorities or the EMA. These modifications may make it more difficult and costly for us to obtain regulatory clearances, approvals or certification for our companion diagnostics or to manufacture, market or distribute our products after clearance, approval or certification is obtained.

We may also be required to conduct additional studies to support a broader claim. Also, to the extent other approved diagnostics are able to broaden their labeling claims to include our approved drug products, we may be forced to abandon any partnered companion diagnostic development plans we undertake or we may not be able to compete effectively upon marketing approval, which could adversely impact our ability to generate revenue from the sale of our approved products and our business operations.

Moreover, even if data from preclinical studies and early clinical trials appear to support development of a companion diagnostic for a product candidate, data generated in later clinical trials may fail to support the analytical and clinical validation of the companion diagnostic. We and our future collaborators may encounter difficulties in developing, obtaining regulatory approval, certification or clearance for, manufacturing and commercializing companion diagnostics similar to those we face with respect to our product candidates themselves, including issues with achieving regulatory clearance or approval, production of sufficient quantities at commercial scale and with appropriate quality standards, and in gaining market acceptance. If we are unable to successfully develop companion diagnostics for our product candidates, or experience delays in doing so, the development of our product candidates may be adversely affected, our product candidates may not obtain marketing approval, and we may not realize the full commercial potential of any of our product candidates that obtain marketing approval. As a result, our business, results of operations and financial condition could be materially harmed. In addition, a diagnostic company with whom we contract may decide to discontinue selling or manufacturing the companion diagnostic test that we anticipate using in connection with development and commercialization of product candidates or our relationship with such diagnostic company may otherwise terminate. We may not be able to enter into arrangements with another diagnostic company to obtain supplies of an alternative diagnostic test for use in connection with the development and commercialization of our product candidates or do so on commercially reasonable terms, which could adversely affect and/or delay the development or commercialization of our product candidates.

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

Because we have limited financial and managerial resources, we focus on specific product candidates, development programs and specific indications. As a result, we may forgo or delay pursuit of opportunities with other product candidates that could have had greater commercial potential. Our resource allocation decisions may cause us to fail to capitalize on viable potential commercial products or profitable market opportunities. Our spending on current and future research and development programs and product candidates for specific indications may not yield any commercially viable product candidates. If we do not accurately evaluate the commercial potential or target market for a particular product candidate, we may relinquish valuable rights to that product candidate through collaborations, licenses and other similar arrangements in cases in which it would have been more advantageous for us to retain sole development and commercialization rights to such product candidate.

We may not be able to obtain or maintain orphan drug designations for any of our product candidates, and we may be unable to maintain the benefits associated with orphan drug designation, including the potential for market exclusivity.

Regulatory authorities in some jurisdictions, including the United States and Europe, may designate drugs or biologics for relatively small patient populations as orphan drugs. Under the Orphan Drug Act of 1983, the FDA may designate a product as an orphan product if it is intended to treat a rare disease or condition, which is generally defined as a patient population of fewer than 200,000 individuals in the United States, or a patient population of greater than 200,000 individuals in the United States, but for which there is no reasonable expectation that the cost of developing the drug will be recovered from sales in the United States. In the European Union (EU), the European Commission grants orphan designation after receiving the opinion of the European Medicines Agency's (EMA) Committee for Orphan Medicinal Products. In the EU, a medicinal product can be designated as an orphan if its sponsor can establish that: (1) the product is intended for the diagnosis, prevention or treatment of a life threatening or chronically debilitating condition (2) either (a) such condition affects not more than five in 10,000 persons in the EU when the application is made, or (b) the product, without the benefits derived from the orphan status, would not generate sufficient return in the EU to justify the necessary investment; and (3) there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorized for marketing in the EU or, if such method exists, the product will be of significant benefit to those affected by that condition.

We have not received orphan drug designation in the United States or the EU for any product candidate. We may seek orphan drug designation in the United States and the EU for TYRA-300 for patients with MIBC and other rare tumors susceptible to an FGFR3 therapy, and similar designations for TYRA-200 and our other product candidates in qualified patient populations. There can be no assurance that the FDA or European Commission will grant orphan designation for any indication for which we apply, or that we will be able to maintain such designation.

In the United States, orphan designation entitles a party to financial incentives such as opportunities for grant funding toward clinical trial costs, tax advantages and user-fee waivers. In addition, if a product candidate that has orphan designation subsequently receives the first FDA approval for the disease for which it has such designation, the product is entitled to orphan drug exclusivity, which means that the FDA may not approve any other applications, including an NDA, to market the same product for the same disease or condition for seven years, except in limited circumstances, such as a showing of clinical superiority to the product with orphan drug exclusivity or where the manufacturer is unable to assure sufficient product quantity. In the EU, orphan designation entitles a party to financial incentives such as reduction of fees, fee waivers, protocol assistance, and access to the centralized marketing authorization procedure. Moreover, upon grant of a marketing authorization and assuming the requirement for orphan designation are also met at the time the marketing authorization is granted, orphan medicinal products are entitled to a ten-year period of market exclusivity for the approved therapeutic indication. The period of

market exclusivity is extended by two years for orphan medicinal products that have also complied with an agreed Pediatric Investigation Plan. The European exclusivity period can be reduced to six years, if, at the end of the fifth year a drug no longer meets the criteria for orphan designation (i.e. the prevalence of the condition has increased above the orphan designation threshold or it is judged that the product is sufficiently profitable so as not to justify maintenance of market exclusivity).

Even if we obtain orphan drug exclusivity for a product, that exclusivity may not effectively protect the product from competition because different drugs can be approved for the same condition. Even after an orphan drug is approved, the FDA or comparable foreign regulatory authorities can subsequently approve the same drug for the same condition if such regulatory authority concludes that the later drug is clinically superior because it is shown to be safer, more effective or makes a major contribution to patient care. Orphan drug exclusivity may also be lost if the FDA later determines that the initial request for designation was materially defective. In addition, orphan drug exclusivity does not prevent the FDA from approving competing drugs for the same or similar disease or condition containing a different active ingredient. In addition, if a subsequent drug is approved for marketing for the same or a similar disease or condition as any of our product candidates that receive marketing approval, we may face increased competition and lose market share regardless of orphan drug exclusivity. Orphan drug designation neither shortens the development time or regulatory review time of a drug nor gives the drug any advantage in the regulatory review or approval process.

If we successfully develop our product candidates, we may seek Breakthrough Therapy designation or Fast Track designation by the FDA for one or more of our product candidates, but we may not receive such designation, and even if we do, such designation may not lead to a faster development or regulatory review or approval process and it does not increase the likelihood that our product candidates will receive marketing approval.

We may seek Breakthrough Therapy or Fast Track designation for some of our product candidates. A Breakthrough Therapy is defined as a drug or biologic that is intended, alone or in combination with one or more other drugs or biologics, to treat a serious or life- threatening disease or condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. For drugs or biologics that have been designated as Breakthrough Therapies, interaction and communication between the FDA and the sponsor of the trial can help to identify the most efficient path for clinical development while minimizing the number of patients placed in ineffective control regimens. An NDA for a Breakthrough Therapy-designated product candidate may also be eligible for rolling review, where the FDA may consider for review sections of the NDA on a rolling basis before the complete application is submitted, if the sponsor provides a schedule for the submission of the sections of the NDA, the FDA agrees to accept sections of the NDA and determines that the schedule is acceptable, and the sponsor pays any required user fees upon submission of the first section of the NDA.

If a product candidate is intended for the treatment of a serious or life-threatening condition and clinical or preclinical data demonstrate the potential to address unmet medical needs for this condition, the sponsor may apply for Fast Track Designation. The sponsor of a Fast Track product candidate has opportunities for more frequent interactions with the applicable FDA review team during product development and an NDA for a Fast Track product candidate may also be eligible for rolling review.

Whether to grant Breakthrough Therapy or Fast Track Designation is within the discretion of the FDA. Accordingly, even if we believe one of our product candidates meets the criteria for these designations, the FDA may disagree and instead determine not to make such designation. In any event, the receipt of either of these designations for a product candidate may not result in a faster development process, review or approval compared to product candidates considered for approval under non-expedited FDA review procedures and does not assure ultimate approval by the FDA. In addition, even if one or more of our product candidates qualify for either of these designations, the FDA may later decide that the product candidate no longer meet the conditions for qualification.

We may in the future conduct clinical trials for certain of our product candidates outside of the United States. However, the FDA and other foreign equivalents may not accept data from such trials, in which case our development plans will be delayed, which could materially harm our business.

We may conduct one or more of our clinical trials for our product candidates outside the United States. Although the FDA may accept data from clinical trials conducted outside the United States, acceptance of this data is subject to certain conditions imposed by the FDA. Where data from foreign clinical trials are intended to as the sole basis for marketing approval in the United States, the FDA will not approve the application on the basis of foreign data alone unless those data are applicable to the U.S. population and U.S. medical practice; the trials were performed by clinical investigators of recognized competence; and the data are considered valid without the need for an on-site inspection by the FDA or, if the FDA considers such an inspection to be necessary, the FDA is able to validate the data through an on-site inspection or other appropriate means. For trials that are conducted only at sites outside of the United States and not subject to an IND, the FDA requires the clinical trial to have been conducted in accordance with GCP and the FDA must be able to validate the data from the clinical trial through an on-site inspection if it deems such inspection necessary. For such trials not subject to an IND, the FDA generally does not review the clinical protocols for the trials, and therefore there is an additional potential risk that the FDA could determine that the trial design or protocol for a non-U.S. clinical trial was inadequate, which could require us to conduct additional clinical trials.

In addition, such foreign trials would be subject to the applicable local laws of the foreign regulatory and legal requirements where the trials are conducted. There can be no assurance the FDA will accept data from clinical trials conducted outside of the United States. If the FDA does not accept data from our clinical trials of our product candidates, it would likely result in the need for additional clinical trials, which would be costly and time consuming and delay or permanently halt our development of our product candidates.

Interim, topline and preliminary data from our preclinical studies and clinical trials that we may announce or publish from time to time may change as more patient data become available and are subject to audit and verification procedures that could result in material changes in the final data.

From time to time, we may publicly disclose preliminary, interim or topline data from our preclinical studies and clinical trials. These interim updates are based on a preliminary analysis of then-available data, and the results and related findings and conclusions are subject to change following a more comprehensive review of the data related to the particular study or trial. For example, we may report responses in certain patients that are unconfirmed at the time and which do not ultimately result in confirmed responses to treatment after follow-up evaluations. We also make assumptions, estimations, calculations and conclusions as part of our analyses of data, and we may not have received or had the opportunity to fully and carefully evaluate all data. As a result, the topline results that we report may differ from future results of the same studies or trials, or different conclusions or considerations may qualify such results, once additional data have been received and fully evaluated. Topline data also remain subject to audit and verification procedures that may result in the final data being materially different from the preliminary data we previously published. As a result, topline data should be viewed with caution until the final data are available. In addition, we may report interim analyses of only certain endpoints rather than all endpoints. Interim data from clinical trials that we may complete are subject to the risk that one or more of the clinical outcomes may materially change as patient enrollment continues and more patient data become available. Adverse changes between interim data and final data could significantly harm our business and prospects. Further, additional disclosure of interim data by us or by our competitors in the future could result in volatility in the price of our common stock.

In addition, the information we choose to publicly disclose regarding a particular study or trial is typically selected from a more extensive amount of available information. Investors may not agree with what we determine is the material or otherwise appropriate information to include in our disclosure, and any information we

determine not to disclose may ultimately be deemed significant with respect to future decisions, conclusions, views, activities or otherwise regarding a particular product candidate or our business. If the interim, topline or preliminary data that we report differ from late, final or actual results, or if others, including regulatory authorities, disagree with the conclusions reached, our ability to obtain approval for, and commercialize, any of our product candidates may be harmed, which could harm our business, financial condition, results of operations and prospects.

We may attempt to secure approval from the FDA through the use of the accelerated approval pathway. If we are unable to obtain such approval, we may be required to conduct additional preclinical studies or clinical trials beyond those that we contemplate, which could increase the expense of obtaining, and delay the receipt of, necessary marketing approvals. Even if we receive accelerated approval from the FDA, if our confirmatory trials do not verify clinical benefit, or if we do not comply with rigorous post-marketing requirements, the FDA may seek to withdraw any accelerated approval we have obtained.

We may in the future seek accelerated approval for our one or more of our product candidates. Under the accelerated approval program, the FDA may grant accelerated approval to a product candidate designed to treat a serious or life-threatening condition that provides meaningful therapeutic benefit over available therapies upon a determination that the product candidate has an effect on a surrogate endpoint or intermediate clinical endpoint that is reasonably likely to predict clinical benefit. The FDA considers a clinical benefit to be a positive therapeutic effect that is clinically meaningful in the context of a given disease, such as irreversible morbidity or mortality. For the purposes of accelerated approval, a surrogate endpoint is a marker, such as a laboratory measurement, radiographic image, physical sign, or other measure that is thought to predict clinical benefit, but is not itself a measure of clinical benefit. An intermediate clinical endpoint is a clinical endpoint that can be measured earlier than an effect on irreversible morbidity or mortality that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit.

The accelerated approval pathway may be used in cases in which the advantage of a new drug over available therapy may not be a direct therapeutic advantage, but is a clinically important improvement from a patient and public health perspective. If granted, accelerated approval is usually contingent on the sponsor's agreement to conduct, in a diligent manner, additional confirmatory studies to verity and describe the drug's clinical benefit. If such post-approval studies fail to confirm the drug's clinical benefit or are not completed in a timely manner, the FDA may withdraw its approval of the drug on an expedited basis. In addition, in December 2022, President Biden signed an omnibus appropriations bill to fund the U.S. government through fiscal year 2023. Included in the omnibus bill is the Food and Drug Omnibus Reform Act of 2022, which among other things, introduced reforms intended to expand the FDA's ability to regulate products receiving accelerated approval, including by increasing the FDA's oversight over the conduct of confirmatory trials; however, the ultimate impact of these reforms remains unclear.

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

Disruptions at the FDA and other government agencies caused by funding shortages or global health concerns could hinder their ability to hire, retain or deploy key leadership and other personnel, or otherwise prevent new or modified products from being developed, approved or commercialized in a timely manner or at all, which could negatively impact our business.

The ability of the FDA and comparable foreign regulatory activities to review and approve new products can be affected by a variety of factors, including government budget and funding levels, statutory, regulatory and policy changes, the FDA's and comparable foreign regulatory activities' ability to hire and retain key personnel and accept the payment of user fees, and other events that may otherwise affect the FDA's and comparable foreign regulatory activities' ability to perform routine functions. Average review times at the FDA and comparable foreign regulatory activities have fluctuated in recent years as a result. In addition, government funding of other government agencies that fund research and development activities is subject to the political process, which is inherently fluid and unpredictable. Disruptions at the FDA and comparable foreign regulatory activities may also slow the time necessary for new drugs and biologics or modifications to approved drugs and biologics to be reviewed and/or approved by necessary government agencies, which would adversely affect our business. For example, over the last several years, including for 35 days beginning on December 22, 2018, the U.S. government has shut down several times and certain regulatory agencies, such as the FDA, have had to furlough critical FDA employees and stop critical activities.

Separately, in response to the COVID-19 pandemic, the FDA postponed most inspections of domestic and foreign manufacturing facilities at various points. Even though the FDA has since resumed standard inspection operations of domestic facilities where feasible, the FDA has continued to monitor and implement changes to its inspectional activities to ensure the safety of its employees and those of the firms it regulates as it adapts to the evolving COVID-19 pandemic, and any resurgence of the virus or emergence of new variants may lead to further inspectional delays.

Regulatory authorities outside the United States have adopted similar restrictions or other policy measures in response to the COVID-19 pandemic. If a prolonged government shutdown occurs, or if global health concerns prevent the FDA or other regulatory authorities from conducting their regular inspections, reviews or other regulatory activities, it could significantly impact the ability of the FDA or comparable foreign regulatory authorities to timely review and process our regulatory submissions, which could have a material adverse effect on our business.

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

As product candidates progress through preclinical studies and clinical trials to marketing approval and commercialization, it is common that various aspects of the development program, such as manufacturing methods and formulation, are altered along the way in an effort to optimize safety, efficacy, yield and manufacturing batch size, minimize costs and achieve consistent quality and results. For example, we changed the delivery vehicle we use in our formulation for TYRA-300 from a cosolvent-based system to an aqueous-based vehicle. While we have observed positive results in a preclinical model using this new delivery vehicle, any further changes in formulation may result in effects and results that are different from those observed in our completed preclinical studies to date. Similarly, in the future we may introduce an alternative formulation of one or more of our product candidates during the course of our ongoing or planned clinical trials. Such changes carry the risk that they will not achieve these intended objectives. Any of these changes could cause our product candidates to perform differently and affect the results of ongoing, planned or future clinical trials conducted with the altered materials. This could delay initiation or completion of clinical trials, require the conduct of bridging studies or clinical trials or the repetition of one or more studies or clinical trials, increase development costs, delay approval of our product candidates and jeopardize our ability to commercialize our product candidates, if approved, and generate revenue.

Risks Related to Our Reliance on Third Parties

We intend to rely on third parties for the manufacture of our product candidates for preclinical and clinical development. This reliance on third parties increases the risk that we will not have sufficient quantities of our product candidates or products or such quantities at an acceptable cost, which could delay, prevent or impair our development or commercialization efforts.

We do not own or operate manufacturing facilities and have no plans to develop our own clinical or commercial-scale manufacturing capabilities. We plan to rely, and expect to continue to rely, on third parties for the manufacture of our product candidates and related raw materials for preclinical and clinical development, as well as for commercial manufacture if any of our product candidates receive marketing approval. The facilities used by third-party manufacturers to manufacture our product candidates must be approved by the FDA or comparable foreign regulatory authorities pursuant to inspections that will be conducted after we submit an NDA to the FDA or any comparable filing to a foreign regulatory authority. We do not control the manufacturing process of, and are completely dependent on, third-party manufacturers for compliance with cGMP or similar foreign requirements for manufacture of products. If these third-party manufacturers cannot successfully manufacture material that conforms to our specifications and the strict regulatory requirements of the FDA or any comparable foreign regulatory authority, they will not be able to secure and/or maintain marketing approval for their manufacturing facilities. In addition, we have no control over the ability of third-party manufacturers to maintain adequate quality control, quality assurance, qualified personnel, and accurate and complete recordkeeping. If the FDA or comparable foreign regulatory authorities does not approve these facilities for the manufacture of our product candidates or if it withdraws any such approval in the future, we may need to find alternative manufacturing facilities, which would significantly impact our ability to develop, obtain marketing approval for or market our product candidates, if approved. Our failure, or the failure of our third-party manufacturers, to comply with applicable regulations could result in sanctions being imposed on us or the third-party manufacturers, including clinical holds, fines, injunctions, civil penalties, delays, suspension or withdrawal of approvals, seizures or recalls of product candidates or products, operating restrictions and criminal prosecutions, any of which could significantly and adversely affect supplies of our products.

Our or a third party's failure to execute on our manufacturing requirements on commercially reasonable terms and in compliance with cGMP or similar foreign requirements (where applicable) could adversely affect our business in a number of ways, including:

- an inability to initiate clinical trials of our product candidates under development;
- delay in submitting regulatory applications, or receiving marketing approvals, for our product candidates;
- subjecting third-party manufacturing facilities or our manufacturing facilities to additional inspections by regulatory authorities;
- requirements to cease development or to recall batches of our product candidates; and
- in the event of approval to market and commercialize our product candidates, an inability to meet commercial demands for our product candidates or any other future product candidates.

In addition, we do not have any long-term commitments or supply agreements with our third party manufacturers. We may be unable to establish any agreements with third-party manufacturers or to do so on acceptable terms, which increases the risk of timely obtaining sufficient quantities of our product candidates or such

quantifies at an acceptable cost. Even if we are able to establish agreements with third-party manufacturers, reliance on third-party manufacturers entails additional risks, including:

- failure of third-party manufacturers to comply with regulatory requirements and maintain quality assurance;
- breach of the manufacturing agreement by the third party;
- failure to manufacture our product according to our specifications;
- failure to manufacture our product according to our schedule or at all;
- misappropriation of our proprietary information, including our trade secrets and know-how; and
- termination or nonrenewal of the agreement by the third party at a time that is costly or inconvenient for us.

Our product candidates and any products that receive marketing approval may compete with the product candidates and products of other companies for access to manufacturing facilities. There are a limited number of manufacturers that operate under cGMP and similar foreign regulations and that might be capable of manufacturing for us. This could lead to a delay in the manufacture of our product candidates or any products that receive marketing approval, and negatively impact the supply of such product candidates or products for clinical trials or commercialization.

Any performance failure on the part of our existing or future manufacturers could delay clinical development or marketing approval, and any related remedial measures may be costly or time consuming to implement. We do not currently have arrangements in place for redundant supply or a second source for all required raw materials used in the manufacture of our product candidates. If our existing or future third-party manufacturers cannot perform as agreed, we may be required to replace such manufacturers and we may be unable to replace them on a timely basis or at all. In particular, any replacement of our manufacturers could require significant effort and expertise because there may be a limited number of qualified replacements. In some cases, the technical skills or technology required to manufacture our product candidates may be unique or proprietary to the original manufacturer and we may have difficulty transferring such skills or technology to another third-party and a feasible alternative may not exist. In addition, certain of our product candidates and our own proprietary methods have never been produced or implemented outside of our company, and we may therefore experience delays to our development programs if and when we attempt to establish new third-party manufacturing arrangements for these product candidates or methods.

Our current and anticipated future dependence upon others for the manufacture of our product candidates or products may adversely affect our future profit margins and our ability to commercialize any products that receive marketing approval on a timely and competitive basis.

Our reliance on third parties requires us to share our confidential information, which increases the possibility that confidential information will be misappropriated or disclosed.

Because we currently plan to rely on third parties to manufacture our product candidates and to perform quality testing, we must, at times, share our proprietary technology and confidential information with them. We seek to protect our proprietary technology, in part, by entering into confidentiality agreements, and, if applicable, material transfer agreements, collaborative research agreements, consulting agreements or other similar agreements with our advisors, employees and consultants prior to beginning research or disclosing proprietary information. These agreements typically limit the rights of the third parties to use or disclose our confidential information. Despite the contractual provisions employed when working with third parties, the need to share confidential information

increases the risk that such trade secrets become known by our competitors, are intentionally or inadvertently incorporated into the technology of others or are disclosed or used in violation of these agreements. Given that our proprietary position is based, in part, on our know-how and confidential information and despite our efforts to protect our confidential information, a competitor's discovery of our proprietary technology and confidential information or other unauthorized use or disclosure would impair our competitive position and may have a material adverse effect on our business, financial condition, results of operations and prospects.

We may seek to enter into collaborations, licenses and other similar arrangements and may not be successful in doing so, and even if we are, we may relinquish valuable rights and may not realize the benefits of such relationships.

We may seek to enter into collaborations, joint ventures, licenses and other similar arrangements for the development or commercialization of our product candidates, due to capital costs required to develop or commercialize the product candidate or manufacturing constraints. We may not be successful in our efforts to establish such collaborations for our product candidates because our research and development pipeline may be insufficient, our product candidates may be deemed to be at too early of a stage of development for collaborative effort or third parties may not view our product candidates as having the requisite potential to demonstrate safety and efficacy or significant commercial opportunity. In addition, we face significant competition in seeking appropriate strategic partners, and the negotiation process can be time-consuming and complex. We may have to relinquish valuable rights to our future revenue streams, research programs or product candidates, or grant licenses on terms that may not be favorable to us, as part of any such arrangement, and such arrangements may restrict us from entering into additional agreements with other potential collaborators. We cannot be certain that, following a collaboration, license or strategic transaction, we will achieve an economic benefit that justifies such transaction.

Even if we are successful in our efforts to establish such collaborations, the terms that we agree upon may not be favorable to us, and we may not be able to maintain such collaborations if, for example, the development or approval of a product candidate is delayed, the safety of a product candidate is questioned or the sales of an approved product candidate are unsatisfactory.

In addition, any potential future collaborations may be terminable by our strategic partners, and we may not be able to adequately protect our rights under these agreements. Furthermore, strategic partners may negotiate for certain rights to control decisions regarding the development and commercialization of our product candidates, if approved, and may not conduct those activities in the same manner as we do. Any termination of collaborations we enter into in the future, or any delay in entering into collaborations related to our product candidates, could delay the development and commercialization of our product candidates and reduce their competitiveness if they reach the market, which could have a material adverse effect on our business, financial condition and results of operations.

We rely on third parties to conduct some of our preclinical studies and will rely on third parties to conduct our clinical trials. If these third parties do not successfully carry out their contractual duties, comply with applicable regulatory requirements or meet expected deadlines, our development programs and our ability to seek or obtain marketing approval for or commercialize our product candidates may be delayed.

We are dependent on third parties to conduct our clinical trials and some of our preclinical studies . Specifically, we have used and relied on, or intend to use and rely on, medical institutions, clinical investigators, CROs, contract development and manufacturing organizations, and consultants to conduct some of our preclinical studies and to conduct clinical trials in accordance with our clinical protocols and regulatory requirements. These CROs, investigators and other third parties play a significant role in the conduct and timing of these preclinical studies and clinical trials and subsequent collection and analysis of data. While we have and will have agreements governing the activities of our CROs, investigators and other third-party contractors, we have limited influence over their actual performance. Nevertheless, we are responsible for ensuring that each of our clinical trials is conducted in

accordance with the applicable protocol and legal, regulatory and scientific standards, and our reliance on our CROs and other third parties does not relieve us of our regulatory responsibilities. We and our CROs are required to comply with GLP and GCP requirements, which are regulations and guidelines enforced by the FDA or comparable foreign regulatory authorities for all of our product candidates in preclinical and clinical development. Regulatory authorities enforce these requirements through periodic inspections of trial sponsors, principal investigators, trial sites, and other third parties. If we or any of our CROs, trial sites or other third parties fail to comply with applicable GLP or GCP or other requirements, the clinical data generated in our clinical trials may be deemed unreliable, and the FDA or comparable foreign regulatory authorities may require us to perform additional preclinical studies or clinical trials before approving our marketing applications. In addition, our clinical trials must be conducted with products produced under cGMP regulations. Our failure to comply with these regulations may require us to repeat clinical trials, which would delay the marketing approval process.

There is no guarantee that any of our CROs, investigators or other third parties will devote adequate time and resources to such trials or perform as contractually required. If any of these third parties fail to meet expected deadlines, adhere to our clinical protocols or meet regulatory requirements, or otherwise performs in a substandard manner, our clinical trials may be extended, delayed or terminated. In addition, many of the third parties with whom we contract may also have relationships with other commercial entities, including our competitors, for whom they may also be conducting clinical trials or other development activities that could harm our competitive position. In addition, principal investigators for our clinical trials may also serve as scientific advisors or consultants to us from time to time and may receive cash or equity compensation in connection with such services. If these relationships and any related compensation result in perceived or actual conflicts of interest, or the FDA concludes that the financial relationship may have affected the interpretation of the study, the integrity of the data generated at the applicable clinical trial site may be questioned and the utility of the clinical trial itself may be jeopardized, which could result in the delay or rejection by the FDA of any NDA we submit. Any such delay or rejection could prevent us from commercializing our product candidates.

Our CROs have the right to terminate their agreements with us in the event of an uncured material breach. In addition, some of our CROs have an ability to terminate their respective agreements with us if we make a general assignment for the benefit of our creditors or if we are liquidated. If any of our relationships with these third parties terminate, we may not be able to enter into arrangements with alternative third parties on commercially reasonable terms or at all. Switching or adding additional CROs, investigators and other third parties involves additional cost and requires our management's time and focus. In addition, there is a natural transition period when a new CRO, investigator or other third party contractor commences work. As a result, delays occur, which can materially impact our ability to meet our desired clinical development timelines. Though we carefully manage our relationships with our CROs, investigators and other third parties, there can be no assurance that we will not encounter challenges or delays in the future or that these delays or challenges will not have a material adverse impact on our business, financial condition and prospects.

Risks Related to Commercialization of Our Product Candidates

Even if we receive marketing approval for any product candidate, we will be subject to ongoing regulatory obligations and continued regulatory review, which may result in significant additional expense. Additionally, our product candidates, if approved, could be subject to labeling and other restrictions on marketing or withdrawal from the market, and we may be subject to penalties if we fail to comply with regulatory requirements or if we experience unanticipated problems with our product candidates, when and if any of them are approved.

Following potential approval of any our product candidates, the FDA may impose significant restrictions on a product's indicated uses or marketing or impose ongoing requirements for potentially costly and time consuming post-approval studies, post-market surveillance or clinical trials to monitor the safety and efficacy of the product, may contain significant limitations related to use restrictions for specified age groups, warnings,

precautions or contraindications, and may include burdensome post-approval study or risk management requirements. For example, the FDA may require a REMS, as a condition of approval of our product candidates, which could include requirements for a medication guide, physician communication plans or additional elements to ensure safe use, such as restricted distribution methods, patient registries and other risk minimization tools. In addition, if the FDA or a comparable foreign regulatory authority approves our product candidates, the manufacturing processes, labeling, packaging, distribution, adverse event reporting, storage, advertising, promotion, import, export recordkeeping, and other activities relating to our products will be subject to extensive and ongoing regulatory requirements. These requirements include submissions of safety and other post-marketing information and reports, registration, as well as continued compliance with cGMP and GCP requirements for any clinical trials that we conduct post- approval. Manufacturers of approved products and their facilities are subject to continual review and periodic, unannounced inspections by the FDA and other regulatory authorities for compliance with cGMP or similar foreign regulations and standards. Later discovery of previously unknown problems with our products, including additional adverse events or adverse events of unanticipated severity or frequency, or with our third-party manufacturers or manufacturing processes, or failure to comply with regulatory requirements, may result in, among other things:

- restrictions on the marketing or manufacturing of our products, withdrawal of the product from the market or product recalls;
- restrictions on product distribution or use, or requirements to conduct post-marketing studies or clinical trials;
- fines, restitutions, disgorgement of profits or revenues, civil money penalties, warning letters, untitled letters or holds on clinical trials;
- refusal by the FDA to approve pending applications or supplements to approved applications filed by us or suspension or revocation of approvals;
- product seizure or detention, or refusal to permit the import or export of our products; and
- injunctions or the imposition of civil or criminal penalties.

The occurrence of any event or penalty described above may inhibit our ability to commercialize our product candidates and generate revenue and could require us to expend significant time and resources in response and could generate negative publicity.

In addition, if any of our product candidates are approved, our product labeling, advertising and promotion will be subject to regulatory requirements and continuing regulatory review. The FDA strictly regulates the promotional claims that may be made about drug products. In particular, a product may not be promoted for uses that are not approved by the FDA as reflected in the product's approved labeling. If we receive marketing approval for a product candidate, physicians may nevertheless, in their independent medical judgment, prescribe it to their patients in a manner that is inconsistent with the approved label. The FDA does not regulate the behavior of physicians in their choice of treatments but the FDA does restrict manufacturer's communications on the subject of off-label use of their products. If we are found to have promoted such off-label uses, we may become subject to significant liability. The FDA, the Department of Justice, and other governmental authorities actively enforce the laws and regulations prohibiting the promotion of off-label uses, and a company that is found to have improperly promoted off-label uses may be subject to significant sanctions. For example, the federal government has levied large civil and criminal fines against companies for alleged improper promotion and has enjoined several companies from engaging in off-label promotion. The FDA has also requested that companies enter into corporate integrity agreements, consent decrees or permanent injunctions under which specified promotional conduct is changed or curtailed.

The FDA's and other regulatory authorities' policies may change and additional government regulations may be enacted that could prevent, limit or delay marketing approval of our product candidates. If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory compliance, we may lose any marketing approval that we may have obtained and we may not achieve or sustain profitability.

We also cannot predict the likelihood, nature or extent of government regulation that may arise from future legislation or administrative or executive action, either in the United States or abroad.

If we are slow or unable to adapt to changes in existing requirements or the adoption of new requirements or policies, or if we are not able to maintain regulatory compliance, we may be subject to enforcement action and we may not achieve or sustain profitability, which would adversely affect our business, prospects, financial condition and results of operations.

The commercial success of our product candidates will depend upon the degree of market acceptance of such product candidates by physicians, patients, healthcare payors and others in the medical community.

Our product candidates may not be commercially successful. Even if any of our product candidates receive marketing approval, they may not gain market acceptance among physicians, patients, healthcare payors or the medical community. The commercial success of any of our current or future product candidates will depend significantly on the broad adoption and use of the resulting product by physicians and patients for approved indications. The degree of market acceptance of our products will depend on a number of factors, including:

- demonstration of clinical efficacy and safety compared to other more-established products;
- the indications for which our product candidates are approved;
- the limitation of our targeted patient population and other limitations or warnings contained in any FDA-approved labeling;
- acceptance of a new drug for the relevant indication by healthcare providers and their patients;
- the pricing and cost-effectiveness of our products, as well as the cost of treatment with our products in relation to alternative treatments and therapies;
- our ability to obtain and maintain sufficient third-party coverage and adequate reimbursement from government healthcare programs, including Medicare and Medicaid, private health insurers and other third-party payors;
- the willingness of patients to pay all, or a portion of, out-of-pocket costs associated with our products in the absence of sufficient third-party coverage and adequate reimbursement;
- any restrictions on the use of our products, and the prevalence and severity of any adverse effects;
- potential product liability claims;
- the timing of market introduction of our products as well as competitive drugs;
- the effectiveness of our or any of our current or potential future collaborators' sales and marketing strategies; and
- unfavorable publicity relating to the product.

If any product candidate is approved but does not achieve an adequate level of acceptance by physicians, hospitals, healthcare payors or patients, we may not generate sufficient revenue from that product and may not become or remain profitable. Our efforts to educate the medical community and third-party payors regarding the benefits of our products may require significant resources and may never be successful.

We currently have no marketing and sales organization and have no experience as a company in commercializing products, and we may have to invest significant resources to develop these capabilities. If we are unable to establish marketing and sales capabilities or enter into agreements with third parties to market and sell our products, we may not be able to generate product revenue.

We have no internal sales, marketing or distribution capabilities, nor have we commercialized a product. If any of our product candidates ultimately receives marketing approval, we must build a marketing and sales organization with technical expertise and supporting distribution capabilities to commercialize each such product in major markets, which will be expensive and time consuming, or collaborate with third parties that have direct sales forces and established distribution systems, either to augment our own sales force and distribution systems or in lieu of our own sales force and distribution systems. We have no prior experience as a company in the marketing, sale and distribution of biopharmaceutical products and there are significant risks involved in building and managing a sales organization, including our ability to hire, retain and incentivize qualified individuals, generate sufficient sales leads, provide adequate training to sales and marketing personnel and effectively manage a geographically dispersed sales and marketing team. Any failure or delay in the development of our internal sales, marketing and distribution capabilities would adversely impact the commercialization of these products. We may not be able to enter into collaborations or hire consultants or external service providers to assist us in sales, marketing and distribution functions on acceptable financial terms, or at all. In addition, our product revenues and our profitability, if any, may be lower if we rely on third parties for these functions than if we were to market, sell and distribute any products that we develop ourselves. We likely will have little control over such third parties, and any of them may fail to devote the necessary resources and attention to sell and market our products effectively. If we are not successful in commercializing our products, either on our own or through arrangements with one or more third parties, we may not be able to generate any future product revenue and we would incur significant additional losses.

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

The availability of coverage and the adequacy of reimbursement by governmental healthcare programs such as Medicare and Medicaid, private health insurers and other third-party payors are essential for most patients to be able to afford prescription medications such as our product candidates, if approved. Our ability to achieve coverage and acceptable levels of reimbursement for our products by third-party payors will have an effect on our ability to successfully commercialize those products. Moreover, we are initially developing TYRA-300 for the treatment of mUC, an indication with a small patient population. In order for products that are designed to treat smaller patient populations to be commercially viable, the reimbursement for such products must be higher, on a relative basis, to account for the lack of volume. Accordingly, we will need to implement a coverage and reimbursement strategy for any approved product candidate with a smaller patient population that accounts for the smaller potential market size. Even if we obtain coverage for a given product by a third-party payor, the resulting reimbursement payment rates may not be adequate or may require co-payments that patients find unacceptably high. For products administered under the supervision of a physician, obtaining coverage and adequate reimbursement may be particularly difficult because of the higher prices often associated with such drugs. Additionally, separate reimbursement for the product itself or the treatment or procedure in which the product is used may not be available, which may impact physician utilization. We cannot be sure that coverage and reimbursement in the United States,

the EU or elsewhere will be available for any product that we may develop, and any reimbursement that may become available may be decreased or eliminated in the future.

Obtaining and maintaining reimbursement status is time consuming, costly and uncertain. The Medicare and Medicaid programs increasingly are used as models for how private payors and other governmental payors develop their coverage and reimbursement policies for drugs. However, no uniform policy for coverage and reimbursement for products exists among third-party payors in the United States. Therefore, coverage and reimbursement for products can differ significantly from payor to payor. As a result, the coverage determination process is often a time consuming and costly process that will require us to provide scientific and clinical support for the use of our products to each payor separately, with no assurance that coverage and adequate reimbursement will be applied consistently or obtained in the first instance. Furthermore, rules and regulations regarding reimbursement change frequently, in some cases at short notice, and we believe that changes in these rules and regulations are likely.

Third-party payors increasingly are challenging prices charged for biopharmaceutical products and services, and many third-party payors may refuse to provide coverage and reimbursement for particular drugs when an equivalent generic drug or a less expensive therapy is available. It is possible that a third-party payor may consider our products as substitutable and only offer to reimburse patients for the less expensive product. Even if we are successful in demonstrating improved efficacy or improved convenience of administration with our products, pricing of existing drugs may limit the amount we will be able to charge for our products. These payors may deny or revoke the reimbursement status of a given product or establish prices for new or existing marketed products at levels that are too low to enable us to realize an appropriate return on our investment in product development. If reimbursement is not available or is available only at limited levels, we may not be able to successfully commercialize our product candidates and may not be able to obtain a satisfactory financial return on products that we may develop, once approved. In addition, in the event that we or third parties develop companion diagnostic tests for use with our product candidates, if approved, such companion diagnostic tests will require coverage and reimbursement separate and apart from the coverage and reimbursement for their companion pharmaceutical or biological products. Similar challenges to obtaining coverage and reimbursement applicable to pharmaceutical or biological products will apply to companion diagnostics tests.

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

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

We face significant competition, and if our competitors develop technologies or product candidates more rapidly than we do or their technologies are more effective, our business and our ability to develop and successfully commercialize products may be adversely affected.

The biotechnology and biopharmaceutical industries are characterized by rapidly advancing technologies, intense competition and a strong emphasis on proprietary and novel products and product candidates. Our competitors have developed, are developing or may develop products or product candidates competitive with our product candidates. Any product candidates that we successfully develop and commercialize will compete with existing therapies and new therapies that may become available in the future. We believe that a significant number of products are currently under development, and may become commercially available in the future, for the treatment of conditions for which we may attempt to develop product candidates. In particular, there is intense competition in the precision oncology field. Our competitors include larger and better-funded pharmaceutical, biopharmaceutical, biotechnological and therapeutics companies. Moreover, we may also compete with universities and other research institutions who may be active in the indications we are targeting and could be in direct competition with us. We also compete with these organizations to recruit management, scientists and clinical development personnel, which could negatively affect our level of expertise and our ability to execute our business plan. We will also face competition in establishing clinical trial sites, enrolling patients for clinical trials and in identifying and in-licensing new product candidates. Smaller or early stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large and established companies.

We expect to face competition from existing products and products in development for each of our product candidates. There are three currently approved pan-FGFR inhibitors: Incyte Corporation's Pemazyre (pemigatinib) and QED Therapeutics' Truseltiq (infigratinib), approved in FGFR2 gene rearrangements in cholangiocarcinoma, and Janssen Biotech, Inc.'s Balversa (erdafitinib), approved in specific FGFR3 and FGFR2 gene alterations. In China, AstraZeneca recently out-licensed their pan-FGFR inhibitor AZD4547 to Abbisko Therapeutics, who are conducting a Phase 2 study in metastatic FGFR3-driven urothelial cancer (NCT05086666). There are a number of other pan-FGFR programs in development for FGFR2 and FGFR3-specific populations, including, among others, Taiho Oncology, Inc.'s TAS-120 (futibatinib), Bayer Pharmaceutical's BAY 1163877 (Rogaratinib), as well as isoform specific FGFR inhibitors such as Relay Therapeutics, Inc.'s RLY-4008, Kinnate Biopharma Inc.'s KIN-3248 and Lilly's Loxo Oncology's recently announced isoform-selective FGFR3 inhibitor compound, LOXO-435 (LOX-24350). BioMarin Pharmaceutical's Voxzogo, a once daily injectable C-naturetic peptide analog was recently approved in the United States for children with achondroplasia who are 5 years of age and older. There are two approved RET inhibitors, Lilly's Loxo Oncology's Retevmo (selpercatinib) and Blueprint Medicines' Gavreto (pralsetinib), as well as programs in development such as Turning Point's TPX-0046 and Boston Pharmaceuticals' BOS172738. There are currently no approved FGFR4 inhibitors, but there are a number of FGFR4 programs in clinical development, including Blueprint Medicines' BLU-554 (fisogatinib), H3 Biomedicines' H3B-6527 and Novartis' FGF401.

Many of our competitors have significantly greater financial, technical, manufacturing, marketing, sales and supply resources or experience than we do. If we successfully obtain marketing approval for any product candidate, we will face competition based on many different factors, including the safety and effectiveness of our products, the ease with which our products can be administered and the extent to which patients accept relatively new routes of administration, the timing and scope of marketing approvals for these products, the availability and cost of manufacturing, marketing and sales capabilities, price, reimbursement coverage and patent position. Competing products could present superior treatment alternatives, including by being more effective, safer, more convenient, less expensive or marketed and sold more effectively than any products we may develop. Competitive products or technological approaches may make any products we develop obsolete or noncompetitive before we recover the expense of developing and commercializing our product candidates. If we are unable to compete effectively, our opportunity to generate revenue from the sale of our products we may develop, if approved, could be adversely affected.

If the market opportunities for our product candidates are smaller than we believe they are, our revenue may be adversely affected, and our business may suffer.

The precise incidence and prevalence for all the conditions we aim to address with our product candidates are unknown. Our projections of both the number of people who have these diseases, as well as the subset of people with these diseases who have the potential to benefit from treatment with our product candidates, are based on our beliefs and estimates. These estimates have been derived from a variety of sources, including the scientific literature, surveys of clinics, patient foundations or market research, and may prove to be incorrect. Further, new trials may change the estimated incidence or prevalence of these indications. The total addressable market across all of our product candidates will ultimately depend upon, among other things, the diagnosis criteria included in the final label for each of our product candidates which receives marketing approval for these indications, the availability of alternative treatments and the safety, convenience, cost and efficacy of our product candidates relative to such alternative treatments, acceptance by the medical community and patient access, drug pricing and reimbursement. The number of patients in the United States and other major markets and elsewhere may turn out to be lower than expected, patients may not be otherwise amenable to treatment with our product candidates or new patients may become increasingly difficult to identify or gain access to, all of which would adversely affect our results of operations and our business. Further, even if we obtain significant market share for our product candidates, because some of our potential target populations are very small, we may never achieve profitability despite obtaining such significant market share.

Our future growth may depend, in part, on our ability to operate in foreign markets, where we would be subject to additional regulatory burdens and other risks and uncertainties.

Our future growth may depend, in part, on our ability to develop and commercialize our product candidates in foreign markets. We are not permitted to market or promote any of our product candidates before we receive marketing approval from applicable regulatory authorities in foreign markets, and we may never receive such marketing approvals for any of our product candidates. To obtain separate marketing approval in many other countries we must comply with numerous and varying regulatory requirements regarding safety and efficacy and governing, among other things, clinical trials, commercial sales, pricing and distribution of our product candidates. If we obtain marketing approval of our product candidates and ultimately commercialize our products in foreign markets, we would be subject to additional risks and uncertainties, including:

- different regulatory requirements for approval of drugs in foreign countries;
- reduced protection for intellectual property rights;
- the existence of additional third-party patent rights of potential relevance to our business;
- unexpected changes in tariffs, trade barriers and regulatory requirements;
- economic weakness, including inflation, political instability or war in particular foreign economies and markets;
- compliance with tax, employment, immigration and labor laws for employees living or traveling abroad;
- foreign currency fluctuations, which could result in increased operating expenses and reduced revenues, and other obligations incident to doing business in another country;
- foreign reimbursement, pricing and insurance regimes;
- workforce uncertainty in countries where labor unrest is common;

- production shortages resulting from any events affecting raw material supply or manufacturing capabilities abroad; and

- business interruptions resulting from geopolitical actions, including war and terrorism, or natural disasters including earthquakes, typhoons, floods and fires.

Risks Related to Our Business Operations and Industry

Our operating results may fluctuate significantly, which makes our future operating results difficult to predict and could cause our operating results to fall below expectations or any guidance we may provide.

Our quarterly and annual operating results may fluctuate significantly, which makes it difficult for us to predict our future operating results. These fluctuations may occur due to a variety of factors, many of which are outside of our control, including, but not limited to:

- the timing and cost of, and level of investment in, research, development, marketing approval and commercialization activities relating to our product candidates, which may change from time to time;

- coverage and reimbursement policies with respect to our product candidates, if approved, and potential future drugs that compete with our products;

- the cost of manufacturing our product candidates, which may vary depending on the quantity of production and the terms of our agreements with third-party manufacturers;

- expenditures that we may incur to acquire, develop or commercialize additional product candidates and technologies;

- the level of demand for any approved products, which may vary significantly;

- future accounting pronouncements or changes in our accounting policies; and

- the timing and success or failure of preclinical studies or clinical trials for our product candidates or competing product candidates, or any other change in the competitive landscape of our industry, including consolidation among our competitors or partners.

The cumulative effects of these factors could result in large fluctuations and unpredictability in our quarterly and annual operating results. As a result, comparing our operating results on a period-to-period basis may not be meaningful. Investors should not rely on our past results as an indication of our future performance.

This variability and unpredictability could also result in our failing to meet the expectations of industry or financial analysts or investors for any period. If our revenue or operating results fall below the expectations of analysts or investors or below any forecasts we may provide to the market, or if the forecasts we provide to the market are below the expectations of analysts or investors, the price of our common stock could decline substantially. Such a stock price decline could occur even when we have met any previously publicly stated revenue or earnings guidance we may provide.

We are dependent on the services of our management and other clinical and scientific personnel, and if we are not able to retain these individuals or recruit additional management or clinical and scientific personnel, our business will suffer.

Our success depends in part on our continued ability to attract, retain, manage and motivate highly qualified management, clinical and scientific personnel. We are highly dependent upon our senior management, as

well as our senior scientists and other members of our management team. The loss of services of any of these individuals could delay or prevent the successful development of our product pipeline, initiation or completion of our preclinical studies and clinical trials or the commercialization of our product candidates. Although we have executed employment agreements or offer letters with each member of our senior management team, these agreements are terminable at will with or without notice and, therefore, we may not be able to retain their services as expected. We do not currently maintain "key person" life insurance on the lives of our executives or any of our employees. This lack of insurance means that we may not have adequate compensation for the loss of the services of these individuals.

We will need to expand and effectively manage our managerial, operational, financial and other resources in order to successfully pursue our clinical development and commercialization efforts. We may not be successful in maintaining our unique company culture and continuing to attract or retain qualified management and scientific and clinical personnel in the future due to the intense competition for qualified personnel among biopharmaceutical, biotechnology and other businesses, particularly in the San Diego County area. Our industry has experienced a high rate of turnover of management personnel in recent years. If we are not able to attract, integrate, retain and motivate necessary personnel to accomplish our business objectives, we may experience constraints that will significantly impede the achievement of our development objectives, our ability to raise additional capital and our ability to implement our business strategy.

We have recently substantially increased, and will need to continue to grow, the size and capabilities of our organization, and we may experience difficulties in managing this growth.

We have substantially increased our organization from four employees as of December 31, 2019 to 38 full-time employees as of March 20, 2023, including 28 employees engaged in research and development. In order to successfully implement our development and commercialization plans and strategies, and as we transition into operating as a public company, we expect to need to continue to add significant additional managerial, operational, sales, marketing, financial and other personnel. Future growth will impose significant added responsibilities on members of management, including:

- identifying, recruiting, integrating, maintaining, retaining and motivating our current and additional employees;
- managing our internal development efforts effectively, including the preclinical, clinical, the FDA or comparable foreign regulatory authorities' review process for product candidates, while complying with any contractual obligations to contractors and other third parties;
- managing increasing operational and managerial complexity; and
- improving our operational, financial and management controls, reporting systems and procedures.

Our future financial performance and our ability to successfully develop and, if approved, commercialize product candidates developed from our FGFR and RET programs and other product candidates will depend, in part, on our ability to effectively manage any future growth, and our management may also have to divert a disproportionate amount of its attention away from day-to-day activities in order to devote a substantial amount of time to managing these growth activities.

If we are not able to effectively expand our organization by hiring new employees and/or engaging additional third-party service providers, we may not be able to successfully implement the tasks necessary to further develop and commercialize TYRA-300, TYRA-200 and any of our other product candidates and, accordingly, may not achieve our research, development and commercialization goals.

We are subject to various federal, state and foreign healthcare laws and regulations, which could increase compliance costs, and our failure to comply with these laws and regulations could harm our results of operations and financial condition.

Our business operations and current and future arrangements with investigators, healthcare professionals, consultants, third-party payors and customers expose us to broadly applicable foreign, federal and state fraud and abuse and other healthcare laws and regulations. These laws may constrain the business or financial arrangements and relationships through which we conduct our operations, including how we research, market, sell and distribute any products for which we obtain marketing approval. Such laws include, without limitation:

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

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

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

- the federal Physician Payments Sunshine Act, which requires certain manufacturers of drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid or the Children's Health Insurance Program (with certain exceptions) to report annually to the Centers for Medicare & Medicaid Services (CMS) information related to payments and other "transfers of value" made to physicians (defined to include doctors, dentists, optometrists, podiatrists and chiropractors), certain non-physician practitioners (physician assistants, nurse practitioners, clinical nurse specialists, certified nurse anesthetists, anesthesiology assistants and certified nurse-midwives) and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members; and

- analogous state and foreign laws and regulations, such as state anti-kickback and false claims laws, may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental third-party payors, including private insurers; some state laws require biopharmaceutical and biotechnology companies to comply with the industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government and may require drug manufacturers to report information related to payments and other transfers of value to physicians and other healthcare providers or marketing expenditures; some state laws that require biopharmaceutical and biotechnology companies to report information

on the pricing of certain drug products; and some state and local laws require the registration or pharmaceutical sales representatives.

Efforts to ensure that our current and future business arrangements with third parties will comply with applicable healthcare laws and regulations will involve ongoing substantial costs. It is possible that governmental authorities will conclude that our business practices, including certain arrangements with physicians who receive stock or stock options as compensation for services provided to us, may not comply with current or future statutes, regulations or case law involving applicable fraud and abuse or other healthcare laws and regulations. If our operations are found to be in violation of any of these laws or any other governmental regulations that may apply to us, we may be subject to significant penalties, including civil, criminal and administrative penalties, damages, fines, disgorgement, imprisonment, exclusion from participation in government funded healthcare programs, such as Medicare and Medicaid, integrity oversight and reporting obligations, contractual damages, reputational harm, diminished profits and future earnings and the curtailment or restructuring of our operations. Defending against any such actions can be costly, time-consuming and may require significant financial and personnel resources. Therefore, even if we are successful in defending against any such actions that may be brought against us, our business may be impaired. Further, if any of the physicians or other healthcare providers or entities with whom we expect to do business is found to be not in compliance with applicable laws, they may be subject to significant criminal, civil or administrative sanctions, including exclusions from government funded healthcare programs.

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

We, our future collaborators and our service providers may be subject to a variety of privacy and data security laws and contractual obligations, which could increase compliance costs and our failure to comply with them could subject us to potentially significant fines or penalties and otherwise harm our business. We are subject to laws and regulations governing the privacy and security of sensitive information, including confidential business and health-related information. The global data protection landscape is rapidly evolving, and we may be affected by or subject to new, amended or existing laws and regulations in the future, including as our operations continue to expand or if we operate in foreign jurisdictions. These laws and regulations may be subject to differing interpretations, which adds to the complexity of processing personal information. Guidance on implementation and compliance practices are often updated or otherwise revised.

In the United States, there are numerous federal and state privacy and data security laws and regulations governing the collection, use, disclosure and protection of personal information, including health information privacy laws, security breach notification laws and consumer protection laws. Each of these laws is subject to varying interpretations and constantly evolving. By way of example, HIPAA imposes privacy and security requirements and breach reporting obligations with respect to individually identifiable health information upon "covered entities" (health plans, health care clearinghouses and certain health care providers), and their respective business associates, individuals or entities that create, received, maintain or transmit protected health information in connection with providing a service for or on behalf of a covered entity, as well as their covered subcontractors. While we do not believe that we are currently acting as a covered entity or business associate under HIPAA and thus are not directly regulated under HIPAA, any person may be prosecuted under HIPAA's criminal provisions either directly or under aiding-and-abetting or conspiracy principles. Consequently, depending on the facts and circumstances, we could be subject to significant penalties if we knowingly receive individually identifiable health information from a HIPAA-covered healthcare provider or research institution that has not satisfied HIPAA's requirements for disclosure of individually identifiable health information.

In addition, certain state laws and regulations govern the privacy, processing and security of health-related and other personal information in certain circumstances, some of which are more stringent than HIPAA and

many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts. By way of example, the California Consumer Privacy Act (CCPA) which went into effect on January 1, 2020, gives California residents certain rights to access and delete their personal information, opt out of certain personal information sharing, and receive detailed information about how their personal information is used. The CCPA provides for civil penalties for violations, as well as a private right of action for data breaches that has increased the likelihood of, and risks associated with data breach litigation. The CCPA may increase our compliance costs and potential liability. Further, the California Privacy Rights Act (CPRA) generally went into effect on January 1, 2023 and significantly amends the CCPA. It imposes further obligations on businesses processing the personal information of California residents, including additional consumer rights processes, limitations on data uses, new audit requirements for higher risk data, and opt outs for certain uses of sensitive data. It also creates a new California data protection agency authorized to issue substantive regulations, which could result in increased privacy and information security enforcement. Additional compliance investment and potential business process changes may be required. Similar laws have passed in Virginia, Colorado, Connecticut and Utah, and have been proposed in other states and at the federal level, reflecting a trend toward more stringent privacy legislation in the United States. The enactment of such laws could have potentially conflicting requirements that would make compliance challenging. In the event that we are subject to or affected by HIPAA, the CCPA, the CPRA or other domestic privacy and data protection laws, any liability from failure to comply with the requirements of these laws could adversely affect our financial condition.

Our operations abroad may also be subject to increased scrutiny or attention from data protection authorities. For example, in Europe, the European Union General Data Protection Regulation, (GDPR) went into effect in May 2018 and imposes strict requirements for processing the personal data of individuals within the European Economic Area (EEA). Companies that must comply with the GDPR face increased compliance obligations and risk, including more robust regulatory enforcement of data protection requirements and potential fines for noncompliance of up to €20 million or 4% of the annual global revenues of the noncompliant company, whichever is greater. Among other requirements, the GDPR regulates transfers of personal data subject to the GDPR to third countries that have not been found to provide adequate protection to such personal data, including the United States; in July 2020, the Court of Justice of the EU (CJEU) limited how organizations could lawfully transfer personal data from the EU/EEA to the United States by invalidating the Privacy Shield for purposes of international transfers and imposing further restrictions on the use of standard contractual clauses (SCCs). In March 2022, the US and EU announced a new regulatory regime intended to replace the invalidated regulations; however, this new EU-US Data Privacy Framework has not been implemented beyond an executive order signed by President Biden on October 7, 2022 on Enhancing Safeguards for United States Signals Intelligence Activities. European court and regulatory decisions subsequent to the CJEU decision of July 16, 2020 have taken a restrictive approach to international data transfers. As supervisory authorities issue further guidance on personal data export mechanisms, including circumstances where the SCCs cannot be used, and/or start taking enforcement action, we could suffer additional costs, complaints and/or regulatory investigations or fines, and/or if we are otherwise unable to transfer personal data between and among countries and regions in which we operate, it could affect the manner in which we provide our services, the geographical location or segregation of our relevant systems and operations, and could adversely affect our financial results.

Further, from January 1, 2021, companies have had to comply with the GDPR and also the UK GDPR, which, together with the amended UK Data Protection Act 2018, retains the GDPR in UK national law. The UK GDPR mirrors the fines under the GDPR, i.e., fines up to the greater of €20 million (£17.5 million) or 4% of global turnover. As we continue to expand into other foreign countries and jurisdictions, we may be subject to additional laws and regulations that may affect how we conduct business. The relationship between the United Kingdom and the European Union in relation to certain aspects of data protection law remains unclear, and it is unclear how United Kingdom data protection laws and regulations will develop in the medium to longer term. The European Commission has adopted an adequacy decision in favor of the United Kingdom, enabling data transfers from EU member states to the United Kingdom without additional safeguards. However, the United Kingdom adequacy

decision will automatically expire in June 2025 unless the European Commission re-assesses and renews or extends that decision.

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

Recently enacted legislation, future legislation and healthcare reform measures may increase the difficulty and cost for us to obtain marketing approval for and commercialize our product candidates and may affect the prices we may set.

In the United States and some foreign jurisdictions, there have been, and we expect there will continue to be, a number of legislative and regulatory changes to the healthcare system, including cost-containment measures that may reduce or limit coverage and reimbursement for newly approved drugs and affect our ability to profitably sell any product candidates for which we obtain marketing approval. In particular, there have been and continue to be a number of initiatives at the U.S. federal and state levels that seek to reduce healthcare costs and improve the quality of healthcare.

For example, in March 2010, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, collectively, the ACA, was enacted in the United States. Among the provisions of the ACA of importance to our potential product candidates, the ACA: established an annual, nondeductible fee on any entity that manufactures or imports specified branded prescription drugs and biologic agents; extended manufacturers' Medicaid rebate liability to covered drugs dispensed to individuals who are enrolled in Medicaid managed care organizations; expanded eligibility criteria for Medicaid programs; expanded the entities eligible for discounts under the 340B drug pricing program; increased the statutory minimum rebates a manufacturer must pay under the Medicaid Drug Rebate Program; created a new Medicare Part D coverage gap discount program; established a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in and conduct comparative clinical effectiveness research, along with funding for such research; and established a Center for Medicare and Medicaid Innovation at CMS to test innovative payment and service delivery models to lower Medicare and Medicaid spending.

Since its enactment, there have been judicial and Congressional challenges to certain aspects of the ACA. On June 17, 2021, the U.S. Supreme Court dismissed the most recent judicial challenge to the ACA brought by several states without specifically ruling on the constitutionality of the ACA. Prior to the Supreme Court's decision, President Biden issued an executive order to initiate a special enrollment period from February 15, 2021 through August 15, 2021 for purposes of obtaining health insurance coverage through the ACA marketplace. The executive order also instructed certain governmental agencies to review and reconsider their existing policies and rules that limit access to healthcare, including among others, reexamining Medicaid demonstration projects and waiver programs that include work requirements, and policies that create unnecessary barriers to obtaining access to health insurance coverage through Medicaid or the ACA.

In addition, other legislative changes have been proposed and adopted since the Affordable Care Act was enacted. On August 2, 2011, the Budget Control Act of 2011 was signed into law, which, among other things, resulted in reductions to Medicare payments to providers, which went into effect on April 1, 2013 and, due to subsequent legislative amendments to the statute, will remain in effect into 2032, with the exception of a temporary suspension from May 1, 2020 through March 31, 2022, unless additional Congressional action is taken. On January

2, 2013, the American Taxpayer Relief Act of 2012 was signed into law, which, among other things, reduced Medicare payments to several providers, including hospitals, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. In March 2021, Congress enacted the American Rescue Plan Act of 2021, which, among other things, eliminated the statutory cap on drug manufacturers' Medicaid Drug Rebate Program rebate liability, effective January 1, 2024. Under current law enacted as part of the ACA, drug manufacturers' Medicaid Drug Rebate Program rebate liability is capped at 100% of the average manufacturer price for a covered outpatient drug.

Further, there has been heightened governmental scrutiny in the United States of pharmaceutical pricing practices in light of the rising cost of prescription drugs. Such scrutiny has resulted in several recent congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to product pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for products. On August 16, 2022, the Inflation Reduction Act of 2022 (IRA) was into law. Among other things, the IRA requires manufacturers of certain drugs to engage in price negotiations with Medicare (beginning in 2026), imposes rebates under Medicare Part B and Medicare Part D to penalize price increases that outpace inflation (first due in 2023), and replaces the Part D coverage gap discount program with a new discounting program (beginning in 2025). The IRA permits the Secretary of the Department of Health and Human Services to implement many of these provisions through guidance, as opposed to regulation, for the initial years. For that and other reasons, it is currently unclear how the IRA will be effectuated. At the state level, legislatures have increasingly passed legislation and implemented regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access and marketing cost disclosure and transparency measures, and, in some cases, designed to encourage importation from other countries and bulk purchasing. Legally mandated price controls on payment amounts by third-party payors or other restrictions could harm our business, results of operations, financial condition and prospects. In addition, regional healthcare authorities and individual hospitals are increasingly using bidding procedures to determine what pharmaceutical products and which suppliers will be included in their prescription drug and other healthcare programs. This could reduce the ultimate demand for our product candidates, if approved, or put pressure on our product pricing, which could negatively affect our business, results of operations, financial condition and prospects.

We expect that these new laws and other healthcare reform measures that may be adopted in the future may result in additional reductions in Medicare and other healthcare funding, more rigorous coverage criteria, new payment methodologies and additional downward pressure on the price that we receive for any approved product. Any reduction in reimbursement from Medicare and other government programs may result in a similar reduction in payments from private payors. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability or commercialize our product candidates, if approved.

We and any of our third-party manufacturers or suppliers may use potent chemical agents and hazardous materials, and any claims relating to improper handling, storage or disposal of these materials could be time consuming or costly.

We and any of our third-party suppliers and potential future collaborators will use biological materials, potent chemical agents and may use hazardous materials, including chemicals and biological agents and compounds that could be dangerous to human health and safety of the environment. Our operations and the operations of our third-party manufacturers and suppliers also produce hazardous waste products. Federal, state and local laws and regulations govern the use, generation, manufacture, storage, handling and disposal of these materials and wastes. Compliance with applicable environmental laws and regulations may be expensive, and current or future environmental laws and regulations may impair our product development efforts. In addition, we cannot eliminate the risk of accidental injury or contamination from these materials or wastes. We do not carry specific biological or

hazardous waste insurance coverage, and our property, casualty and general liability insurance policies specifically exclude coverage for damages and fines arising from biological or hazardous waste exposure or contamination. In the event of contamination or injury, we could be held liable for damages or be penalized with fines in an amount exceeding our resources, and our clinical trials or marketing approvals could be suspended.

Although we maintain workers' compensation insurance for certain costs and expenses we may incur due to injuries to our employees resulting from the use of hazardous materials or other work-related injuries, this insurance may not provide adequate coverage against potential liabilities. We do not maintain insurance for toxic tort claims that may be asserted against us in connection with our storage or disposal of biologic, hazardous or radioactive materials.

In addition, we may incur substantial costs in order to comply with current or future environmental, health and safety laws and regulations, which have tended to become more stringent over time. These current or future laws and regulations may impair our research, development or production efforts. Failure to comply with these laws and regulations also may result in substantial fines, penalties or other sanctions or liabilities, which could materially adversely affect our business, financial condition, results of operations and prospects.

If product liability lawsuits are brought against us, we may incur substantial liabilities and may be required to limit commercialization of our products.

We face an inherent risk of product liability as a result of the clinical trials of our product candidates and will face an even greater risk if we commercialize our product candidates. For example, we may be sued if our product candidates allegedly cause injury or are found to be otherwise unsuitable during product testing, manufacturing, marketing or sale. Any such product liability claims may include allegations of defects in manufacturing, defects in design, a failure to warn of dangers inherent in the product candidate, negligence, strict liability and a breach of warranties. Claims may be brought against us by clinical trial participants, patients or others using, administering or selling products that may be approved in the future. Claims could also be asserted under state consumer protection acts.

If we cannot successfully defend ourselves against product liability claims, we may incur substantial liabilities or be required to limit or cease the commercialization of our products. Even a successful defense would require significant financial and management resources. Regardless of the merits or eventual outcome, liability claims may result in:

- decreased demand for our products, if approved;
- injury to our reputation and significant negative media attention;
- withdrawal of clinical trial participants;
- costs to defend the related litigation;
- a diversion of our management's time and our resources;
- substantial monetary awards to trial participants or patients;
- product recalls, withdrawals or labeling, marketing or promotional restrictions;
- significant negative financial impact;
- the inability to commercialize our product candidates; and
- a decline in our stock price.

We currently hold $10 million of product liability insurance coverage. We may need to increase our insurance coverage as we initiate additional clinical trials or if we commence commercialization of our product candidates, if ever. Insurance coverage is increasingly expensive. Our inability to obtain and retain sufficient product liability insurance at an acceptable cost to protect against potential product liability claims could prevent or inhibit the commercialization of our product candidates. Although we maintain such insurance, any claim that may be brought against us could result in a court judgment or settlement in an amount that is not covered, in whole or in part, by our insurance or that is in excess of the limits of our insurance coverage. Our insurance policies will also have various exclusions, and we may be subject to a product liability claim for which we have no coverage. We may have to pay any amounts awarded by a court or negotiated in a settlement that exceed our coverage limitations or that are not covered by our insurance, and we may not have, or be able to obtain, sufficient capital to pay such amounts.

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

We do not carry insurance for all categories of risk that our business may encounter, including product liability insurance. Some of the policies we currently maintain include property, general liability, employment benefits liability, business automobile workers' compensation, directors' and officers', employment practices and fiduciary liability insurance. We do not know, however, if we will be able to maintain insurance with adequate levels of coverage. Any significant uninsured liability may require us to pay substantial amounts, which would adversely affect our financial position and results of operations.

We and any of our potential future collaborators will be required to report to regulatory authorities if any of our product candidates or approved products in clinical trials cause or contribute to certain adverse medical events, and any failure to do so would result in sanctions that would materially harm our business.

The FDA or comparable foreign regulatory authorities would require that we and potential future collaborators report certain information about adverse medical events relating to any product that is approved or product candidate in clinical trials. The timing of our obligation to report would be triggered by the date we become aware of the adverse event as well as the nature of the event. We and any of our potential future collaborators or CROs may fail to report adverse events within the prescribed timeframe. If we or any of our potential future collaborators or CROs fail to comply with such reporting obligations, the FDA or a comparable foreign regulatory authority could take action, including criminal prosecution, the imposition of civil monetary penalties, seizure of our products or delay in approval or clearance of future products.

Our information technology systems, or those of any of our CROs, other contractors or consultants or potential future collaborators, may fail or suffer security breaches, which could result in a material disruption of our product development programs, harm our reputation, significant fines, penalties and liability and loss of customers or sales.

In the ordinary course of business, we collect, store, transmit and otherwise process large amounts of data including, without limitation, proprietary business information and personal information. Despite the implementation of security measures, our information technology systems (including infrastructure) and those of our current and any future CROs and other contractors, consultants and collaborators are vulnerable to attack, damage or interruption from computer viruses and malware (e.g. ransomware), malicious code, cybersecurity threats (such as denial-of-service attacks, cyberattacks or cyber-intrusions over the Internet, hacking, phishing and other social engineering attacks), fraud, sophisticated nation-state and nation-state-supported actors, unauthorized access or use, natural disasters, terrorism, war, such as the conflict between Russia and Ukraine, and telecommunication and electrical failures. Our systems are also subject to compromise from internal threats, such as theft, misuse, unauthorized access or other improper or accidental actions by employees, vendors and other third parties with

otherwise legitimate access to our systems. Third parties may also attempt to fraudulently induce our employees and contractors into disclosing sensitive information such as usernames, passwords or other information, or otherwise compromise the security of our electronic systems, networks, and/ or physical facilities in order to gain access to our data.

Given the unpredictability of the timing, nature and scope of information technology disruptions, there can be no assurance that any security procedures and controls that we or our third-party partners and service providers have implemented will be sufficient to prevent cyberattacks from occurring. The latency of a compromise is often measured in months, but could be years, and we may not be able to detect a compromise in a timely manner. New techniques may not be identified until they are launched against a target, and we may be unable to anticipate these techniques or detect an incident, assess its severity or impact, react or appropriately respond in a timely manner or implement adequate preventative measures, resulting in potential data loss or other damage to our information technology systems.

We and certain of our service providers are from time to time subject to cyberattacks and security incidents. While we do not believe that we have experienced any significant system failure, accident or security breach to date, if such an event were to occur and cause interruptions in our or our third party service provider's operations or result in the unauthorized disclosure of or access to personally identifiable information or individually identifiable health information (violating certain privacy laws such as GDPR), it could result in a material disruption of our development programs and our business operations, whether due to a loss of our trade secrets or other similar disruptions. Some of the federal, state and foreign government requirements include obligations of companies to notify individuals, governmental authorities, supervisory bodies, the media and other parties of security breaches involving particular personally identifiable information, which could result from breaches experienced by us or by our vendors, contractors, or organizations with which we have formed strategic relationships. Also, due to the COVID-19 pandemic, and continued hybrid working environment, many of our employees are working remotely. As a result, we may have increased cyber security and data security risks, due to increased use of home wi-fi networks and virtual private networks, as well as increased disbursement of physical machines. While we implement IT controls to reduce the risk of a cyber security or data security breach, there is no guarantee that these measures will be adequate to safeguard all systems, especially with an increased number of employees working remotely.

Any security breach or other incident, whether real or perceived, could impact our reputation, impact the integrity of our data, cause us to incur significant costs, including legal expenses, harm customer confidence, hurt our expansion into new markets, cause us to incur remediation costs, or cause us to lose existing customers. For example, the loss of clinical trial data from clinical trials could result in delays in our marketing approval efforts and significantly increase our costs to recover or reproduce the data. We also rely on third parties to manufacture our product candidates, and similar events relating to their computer systems could also have a material adverse effect on our business. To the extent that any real or perceived disruption or security breach affects our systems (or those of our third-party collaborators, service providers, contractors or consultants) or were to result in a loss of or accidental, unlawful or unauthorized access to, use of, release of, or other processing of personal information, or damage to, our data or applications, or inappropriate disclosure of confidential or proprietary information, we could incur liability, the further development and commercialization of our product candidates could be delayed, and we could be subject to significant fines, penalties or liabilities for any noncompliance to certain privacy and security laws. We maintain cyber liability insurance; however, this insurance may not be sufficient to cover the financial, legal, business or reputational losses that may result from an interruption or breach of our systems.

Our business is subject to risks arising from COVID-19 and other epidemic diseases.

A public health pandemic, such as COVID-19 has the potential to present substantial public health and economic challenges and affect our employees, patients, physicians and other healthcare providers, communities and business operations, as well as the U.S. and global economies and financial markets. A pandemic, including

COVID-19, or other public health epidemic, poses the risk that we or our employees, contractors, including our CROs, suppliers, collaborators and other partners may be prevented from conducting business activities for an indefinite period of time, including due to spread of the disease within these groups or due to shutdowns that may be requested or mandated by governmental authorities. International and U.S. governmental authorities in impacted regions have taken and may continue to take actions in an effort to slow the spread of COVID-19, including issuing varying forms of "stay-at-home" orders, and restricting business functions outside of one's home. While it is not possible at this time to estimate the impact that COVID-19 could have on our business in the future, particularly as we advance our product candidates to clinical development, the continued spread of COVID-19 and the measures taken by the governmental authorities, and any future epidemic disease outbreaks, could: disrupt the supply chain and the manufacture or shipment of drug substances and finished drug products for our product candidates for use in our research, preclinical studies and clinical trials, delay, limit or prevent our employees and CROs from continuing research and development activities; impede our clinical trial initiation and recruitment and the ability of patients to continue in clinical trials, including the risk that participants enrolled in our clinical trials will contract COVID-19 or other epidemic diseases while the clinical trial is ongoing, which could impact the results of the clinical trial, including by increasing the number of observed adverse events; and impede testing, monitoring, data collection and analysis and other related activities, any of which could delay our preclinical studies and clinical trials and increase our development costs, and have a material adverse effect on our business, financial condition and results of operations. The COVID-19 pandemic and any future epidemic disease could also potentially affect the business of the FDA or comparable foreign regulatory authorities, which could result in delays in meetings related to planned or ongoing clinical trials. The COVID-19 pandemic and mitigation measures have had and may continue to have, and any future epidemic disease outbreak may have, an adverse impact on global economic conditions which could have an adverse effect on our business and financial condition, including impairing our ability to raise capital when needed. The extent to which the COVID-19 pandemic or any future epidemic disease impacts our results will depend on future developments that are highly uncertain and cannot be predicted.

Our business could be affected by litigation, government investigations and enforcement actions.

We operate in a highly regulated industry and we could be subject to litigation, government investigation and enforcement actions on a variety of matters in the United States or foreign jurisdictions, including, without limitation, intellectual property, regulatory, product liability, environmental, whistleblower, false claims, privacy, anti-kickback, anti-bribery, securities, commercial, employment and other claims and legal proceedings which may arise from conducting our business. Any determination that our operations or activities are not in compliance with existing laws or regulations could result in the imposition of fines, civil and criminal penalties, product seizure, equitable remedies, including disgorgement, injunctive relief and/or other sanctions against us, and remediation of any such findings could have an adverse effect on our business operations.

Legal proceedings, government investigations and enforcement actions can be expensive and time consuming. An adverse outcome resulting from any such proceeding, investigations or enforcement actions could result in significant damages awards, fines, penalties, exclusion from the federal healthcare programs, healthcare or regulatory debarment, injunctive relief, product recalls, reputational damage and modifications of our business practices, which could have a material adverse effect on our business and results of operations.

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

We are exposed to the risk that our employees and independent contractors, including principal investigators, CROs, consultants and vendors may engage in misconduct or other illegal activity. Misconduct by these parties could include intentional, reckless and/or negligent conduct or disclosure of unauthorized activities to us that violate: (i) the laws and regulations of the FDA and other similar regulatory requirements, including those

laws that require the recording and reporting of true, complete and accurate information to such authorities, (ii) manufacturing standards, including cGMP requirements, (iii) federal and state data privacy, security, fraud and abuse and other healthcare laws and regulations in the United States and abroad or (iv) laws that require the true, complete and accurate reporting of financial information or data. Activities subject to these laws also involve the improper use or misrepresentation of information obtained in the course of clinical trials, the creation of fraudulent data in our preclinical studies or clinical trials or illegal misappropriation of drug product, which could result in regulatory consequences or sanctions and cause serious harm to our reputation. It is not always possible to identify and deter misconduct by employees and other third parties, and the precautions we take to detect and prevent this activity may not be effective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to be in compliance with such laws or regulations. In addition, we are subject to the risk that a person or government could allege such fraud or other misconduct, even if none occurred. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business and financial results, including, without limitation, the imposition of significant civil, criminal and administrative penalties, damages, monetary fines, disgorgements, possible exclusion from participation in Medicare, Medicaid and other federal healthcare programs, imprisonment, contractual damages, reputational harm, diminished profits and future earnings, additional reporting requirements and oversight if we become subject to a corporate integrity agreement or similar agreement to resolve allegations of non-compliance with these laws and curtailment of our operations, any of which could adversely affect our ability to operate our business and our results of operations.

We may engage in strategic transactions that could impact our liquidity, increase our expenses and present significant distractions to our management.

From time to time, we may consider strategic transactions, such as acquisitions of companies, asset purchases and out-licensing or in-licensing of intellectual property, products or technologies. Additional potential transactions that we may consider in the future include a variety of business arrangements, including spin-offs, strategic partnerships, joint ventures, restructurings, divestitures, business combinations and investments. Any future transactions could increase our near and long-term expenditures, result in potentially dilutive issuances of our equity securities, including our common stock, or the incurrence of debt, contingent liabilities, amortization expenses or acquired in-process research and development expenses, any of which could affect our financial condition, liquidity and results of operations. Future acquisitions may also require us to obtain additional financing, which may not be available on favorable terms or at all. These transactions may never be successful and may require significant time and attention of our management. In addition, the integration of any business that we may acquire in the future may disrupt our existing business and may be a complex, risky and costly endeavor for which we may never realize the full benefits of the acquisition. Accordingly, although there can be no assurance that we will undertake or successfully complete any additional transactions of the nature described above, any additional transactions that we do complete could have a material adverse effect on our business, results of operations, financial condition and prospects.

Unstable market and economic conditions and adverse developments with respect to financial institutions and associated liquidity risk may have serious adverse consequences on our business, financial condition and stock price.

The global credit and financial markets have recently experienced extreme volatility and disruptions, including severely diminished liquidity and credit availability, declines in consumer confidence, declines in economic growth, increases in unemployment rates and uncertainty about economic stability. The financial markets and the global economy may also be adversely affected by the current or anticipated impact of military conflict, including the conflict between Russia and Ukraine, terrorism or other geopolitical events. Sanctions imposed by the United States and other countries in response to such conflicts, including the one in Ukraine, may also adversely impact the financial markets and the global economy, and any economic countermeasures by affected countries and

others could exacerbate market and economic instability. More recently, the closures of SVB and Signature Bank and their placement into receivership with the FDIC created bank-specific and broader financial institution liquidity risk and concerns. Although the Department of the Treasury, the Federal Reserve, and the FDIC jointly released a statement that depositors at SVB and Signature Bank would have access to their funds, even those in excess of the standard FDIC insurance limits, under a systemic risk exception, future adverse developments with respect to specific financial institutions or the broader financial services industry may lead to market-wide liquidity shortages, impair the ability of companies to access near-term working capital needs, and create additional market and economic uncertainty. There can be no assurance that future credit and financial market instability and a deterioration in confidence in economic conditions will not occur. Our general business strategy may be adversely affected by any such economic downturn, liquidity shortages, volatile business environment or continued unpredictable and unstable market conditions. If the equity and credit markets deteriorate, or if adverse developments are experienced by financial institutions, it may cause short-term liquidity risk and also make any necessary debt or equity financing more difficult, more costly, more onerous with respect to financial and operating covenants and more dilutive. Failure to secure any necessary financing in a timely manner and on favorable terms could have a material adverse effect on our growth strategy, financial performance and stock price and could require us to delay or abandon clinical development plans. In addition, there is a risk that one or more of our current service providers, financial institutions, manufacturers and other partners may be adversely affected by the foregoing risks, which could directly affect our ability to attain our operating goals on schedule and on budget.

Changes in tax law may materially adversely affect our financial condition, results of operations and cash flows.

New income, sales, use or other tax laws, statutes, rules, regulations or ordinances could be enacted at any time, or interpreted, changed, modified or applied adversely to us, any of which could adversely affect our business operations and financial performance. For example, the Tax Cuts and Jobs Act of 2017 amended Section 174 of the United States Internal Revenue Code of 1986, as amended (Code), such that in taxable years beginning after December 31, 2021, expenditures that are incurred for research and development in the U.S. will be capitalized and amortized, which may have an adverse effect on our cash flow. The likelihood of specific changes in tax law being enacted or implemented is unclear. We are currently unable to predict whether such changes will occur. If such changes are enacted or implemented, we are currently unable to predict the ultimate impact on our business. We urge our investors to consult with their legal and tax advisors with respect to any changes in tax law and the potential tax consequences of investing in our common stock.

Our ability to use net operating loss carryforwards and other tax attributes may be limited in connection with our initial public offering or other ownership changes.

We have incurred substantial losses during our history, do not expect to become profitable in the near future and may never achieve profitability. To the extent that we continue to generate taxable losses, unused losses will, subject to limitations, carry forward to offset future taxable income, if any, until such unused losses expire (if at all). At December 31, 2022, we had federal and state net operating loss (NOL) carryforwards of approximately $46.0 million and $35.9 million, respectively.

Federal NOL carryforwards generated in periods after December 31, 2017 may be carried forward indefinitely. The ability to use federal NOL carryforwards to offset taxable income, particularly for tax years beginning after December 31, 2020, may be limited.

In addition, our NOL carryforwards are subject to review and possible adjustment by the United States Internal Revenue Service, and state tax authorities. Under Section 382 of the Code, our federal NOL carryforwards may become subject to an annual limitation in the event of certain cumulative changes in the ownership of our company. An “ownership change” pursuant to Section 382 of the Code generally occurs if one or more stockholders or groups of stockholders who own at least 5% of a company’s stock increase their ownership by more than 50

percentage points over their lowest ownership percentage within a rolling three-year period. Our ability to utilize our NOL carryforwards and other tax attributes to offset future taxable income or tax liabilities may be limited as a result of ownership changes. Similar rules may apply under state tax laws. We have not yet determined the amount of the cumulative change in our ownership resulting from our initial public offering (IPO) or other transactions, or any resulting limitations on our ability to utilize our NOL carryforwards and other tax attributes. If we earn taxable income, such limitations could result in increased future income tax liability to us and our future cash flows could be adversely affected. We have recorded a full valuation allowance related to our NOL carryforwards and other deferred tax assets due to the uncertainty of the ultimate realization of the future benefits of those assets.

Risks Related to Our Intellectual Property

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

Our success depends in large part on our ability to obtain and maintain patent protection in the United States and other countries with respect to our product candidates and other proprietary technologies we may develop as well as our ability to operate without infringing upon the proprietary rights of others. We seek to protect our proprietary position, in part, by filing patent applications in the United States and abroad relating to our product candidates and other proprietary technologies we may develop. If we are unable to obtain or maintain patent protection with respect to our product candidates and other proprietary technologies we may develop, our business, financial condition, results of operations and prospects could be materially harmed.

Changes in either the patent laws or their interpretation in the United States and other countries may diminish our ability to protect our inventions, obtain, maintain and enforce our intellectual property rights and, more generally, could affect the value of our intellectual property or narrow the scope of our protection. We cannot predict whether the patent applications we are currently pursuing will issue as patents in any particular jurisdiction or whether the claims of any issued patents will provide sufficient protection against competitors or other third parties.

The patent prosecution process is expensive, time-consuming, and complex, and we may not be able to file, prosecute, maintain, enforce, or license all necessary or desirable patent applications at a reasonable cost or in a timely manner. It is also possible that we will fail to identify patentable aspects of our research and development output in time to obtain patent protection. Although we enter into non-disclosure and confidentiality agreements with parties who have access to confidential or patentable aspects of our research and development output, such as our employees, CROs, consultants, advisors and other third parties, any of these parties may breach the agreements and disclose such output before a patent application is filed, thereby jeopardizing our ability to seek patent protection. In addition, our ability to obtain and maintain valid and enforceable patents depends on whether the differences between our inventions and the prior art allow our inventions to be patentable over the prior art. Furthermore, publications of discoveries in the scientific literature often lag behind the actual discoveries, and patent applications in the United States and other jurisdictions are typically not published until 18 months after filing, or in some cases not at all. Therefore, we cannot be certain that we were the first to make the inventions claimed in any of our pending patent applications, or that we were the first to file for patent protection of such inventions.

The patent position of biopharmaceutical and biotechnology companies generally is highly uncertain, involves complex legal and factual questions and has been the subject of much litigation in recent years. As a result, the issuance, scope, validity, enforceability and commercial value of our patent rights are highly uncertain. Our patent applications may not result in patents being issued which protect our product candidates and other proprietary

technologies we may develop or which effectively prevent others from commercializing competitive technologies and products.

Moreover, the claim coverage in a patent application can be significantly reduced before the patent is granted. Even if our patent applications issue as patents, they may not issue in a form that will provide us with any meaningful protection, prevent competitors or other third parties from competing with us or otherwise provide us with any competitive advantage. Any patents issuing from our patent applications may be challenged, narrowed, circumvented or invalidated by third parties. Consequently, we do not know whether our product candidates and other proprietary technology will be protectable or remain protected by valid and enforceable patents. Even if a patent is granted, our competitors or other third parties may be able to circumvent the patent by developing similar or alternative technologies or products in a non-infringing manner which could materially adversely affect our business, financial condition, results of operations and prospects. In addition, given the amount of time required for the development, testing and regulatory review of our product candidates, patents protecting the product candidates might expire before or shortly after such product candidates are commercialized. As a result, our intellectual property may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours.

The issuance of a patent is not conclusive as to its inventorship, scope, validity, or enforceability and our patents may be challenged in the courts or patent offices in the United States and abroad. We may be subject to a third-party pre-issuance submission of prior art to the United States Patent and Trademark Office (USPTO) or become involved in opposition, derivation, revocation, reexamination, post- grant and inter partes review, or other similar proceedings challenging our patent rights. An adverse determination in any such submission, proceeding or litigation could reduce the scope of, or invalidate or render unenforceable, our patent rights, allow third parties to commercialize our product candidates and other proprietary technologies we may develop and compete directly with us, without payment to us, or result in our inability to manufacture or commercialize products without infringing third-party patent rights. Such proceedings also may result in substantial cost and require significant time from our scientists and management, even if the eventual outcome is favorable to us.

We do not own or license any issued patents and substantive examination has not begun on any of our pending patent applications, which makes it is difficult to forecast the extent of any future patent right.

We cannot be certain that the claims in our U.S. pending patent applications or corresponding international patent applications, or patent applications in certain foreign territories, will be considered patentable by the USPTO. Patent claims are subject to revision during prosecution and pending patent applications cannot be enforced against third parties practicing the technology claimed in such applications unless, and until, patents issue from such applications, and then only to the extent the issued claims cover the third party's technology. There can be no assurance that our patent applications will result in patents being issued or that issued patents will afford sufficient protection against competitors with similar technology. At present, we have filed U.S. provisional patent applications, a U.S. nonprovisional patent application, a European patent application, international patent applications under the PCT and Taiwan patent applications. None of our patent applications have entered substantive examination by a patent office, which makes it impossible at this time to gauge which art will be cited by examiners or the extent of any rejections we may receive. For example, examiners at a patent office may uncover prior art of which we were not previously aware, and if this cited prior art encompasses our claimed inventions, it may restrict patentability or prevent allowance of any pending patent claims. Furthermore, the patent prosecution process is expensive, time-consuming, and often a multi-year process. We and any future licensors may not be able to file and prosecute all necessary or desirable patent applications at a reasonable cost or in a timely manner or in all jurisdictions where protection may be commercially advantageous. Therefore, we cannot be certain that we will own any issued patents or develop a patent portfolio, which could have a material adverse effect on our business, financial condition, results of operations, and prospects.

We may not be able to protect our intellectual property and proprietary rights throughout the world.

Filing, prosecuting and defending patents on our product candidates and other proprietary technologies we may develop in all countries throughout the world would be prohibitively expensive, and the laws of foreign countries may not protect our rights to the same extent as the laws of the United States. Consequently, we may not be able to prevent third parties from practicing our inventions in all countries outside the United States, or from selling or importing products made using our inventions in and into the United States or other jurisdictions. Competitors may use our technologies in jurisdictions where we have not obtained patent protection to develop their own products and, further, may export otherwise infringing products to territories where we have patent protection but enforcement is not as strong as that in the United States. These products may compete with our product candidates, and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing.

Many companies have encountered significant problems in protecting and defending intellectual property rights in foreign jurisdictions. The legal systems of certain countries, particularly certain developing countries, do not favor the enforcement of patents, trade secrets and other intellectual property protection, particularly those relating to biotechnology and pharmaceutical products, which could make it difficult for us to stop the infringement of our patents or marketing of competing products in violation of our intellectual property and proprietary rights generally. In India, unlike the United States, there is no link between regulatory approval for a drug and its patent status. In addition, some jurisdictions, such as Europe, Japan and China, may have a higher standard for patentability than in the United States, including, for example, the requirement of claims having literal support in the original patent filing and the limitation on using supporting data that is not in the original patent filing. Under those heightened patentability requirements, we may not be able to obtain sufficient patent protection in certain jurisdictions even though the same or similar patent protection can be secured in U.S. and other jurisdictions.

In addition, geo-political actions in the United States and in foreign countries could increase the uncertainties and costs surrounding the prosecution or maintenance of our patent applications or those of any current or future licensors and the maintenance, enforcement or defense of future issued patents or those of any future licensors. For example, the United States and foreign government actions related to Russia's war with Ukraine may limit or prevent filing, prosecution, and maintenance of patent applications in Russia. Government actions may also prevent maintenance of issued patents in Russia. In addition, a decree was adopted by the Russian government in March 2022, allowing Russian companies and individuals to exploit inventions owned by patentees from the United States without consent or compensation. Consequently, we would not be able to prevent third parties from practicing our inventions in Russia or from selling or importing products made using our inventions in and into Russia. Accordingly, our competitive position may be impaired, and our business, financial condition, results of operations and prospects may be adversely affected.

Proceedings to enforce our intellectual property and proprietary rights in foreign jurisdictions could result in substantial costs and divert our efforts and attention from other aspects of our business, could put our patents at risk of being invalidated or interpreted narrowly, could put our patent applications at risk of not issuing and could provoke third parties to assert claims against us. We may not prevail in any lawsuits that we initiate, and the damages or other remedies awarded, if any, may not be commercially meaningful. Accordingly, our efforts to enforce our intellectual property and proprietary rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop.

Many countries have compulsory licensing laws under which a patent owner may be compelled to grant licenses to third parties. In addition, many countries limit the enforceability of patents against government agencies or government contractors. In these countries, the patent owner may have limited remedies, which could materially diminish the value of such patent. If we are forced to grant a license to third parties with respect to any patents

relevant to our business, our competitive position may be impaired, and our business, financial condition, results of operations and prospects may be adversely affected.

Finally, Europe's planned Unified Patent Court may in particular present uncertainties for our ability to protect and enforce our patent rights against competitors in Europe. In 2012, the European Patent Package, or EU Patent Package, regulations were passed with the goal of providing a single pan-European Unitary Patent and a new European Unified Patent Court (UPC) for litigation involving European patents. Implementation of the EU Patent Package will likely occur in the first half of 2023. Under the UPC, all European patents, including those issued prior to ratification of the European Patent Package, will by default automatically fall under the jurisdiction of the UPC. The UPC will provide our competitors with a new forum to centrally revoke our European patents, and allow for the possibility of a competitor to obtain pan-European injunctions. It will be several years before we will understand the scope of patent rights that will be recognized and the strength of patent remedies that will be provided by the UPC. Under the EU Patent Package as currently proposed, we will have the right to opt our patents out of the UPC over the first seven years of the court's existence, but doing so may preclude us from realizing the benefits of the new unified court.

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

Periodic maintenance fees, renewal fees, annuity fees, and various other government fees on patents and applications will be due to be paid to the USPTO and various government patent agencies outside of the United States over the lifetime of our patents and applications. The USPTO and various non-U.S. government agencies require compliance with several procedural, documentary, fee payment and other similar provisions during the patent application process. In some cases, an inadvertent lapse can be cured by payment of a late fee or by other means in accordance with the applicable rules. There are situations, however, in which non-compliance can result in abandonment or lapse of the patent or patent application, resulting in a partial or complete loss of patent rights in the relevant jurisdiction. In such an event, potential competitors might be able to enter the market with similar or identical products or technology, which could have a material adverse effect on our business, financial condition, results of operations, and prospects.

Changes in U.S. patent law could diminish the value of patents in general, thereby impairing our ability to protect our products.

Changes in either the patent laws or interpretation of the patent laws in the United States could increase the uncertainties and costs surrounding the prosecution of patent applications and the enforcement or defense of issued patents. Since March 2013, under the Leahy-Smith America Invents Act (the America Invents Act) enacted in September 2011, the United States transitioned to a first inventor to file system in which, assuming that other requirements for patentability are met, the first inventor to file a patent application will be entitled to the patent on an invention regardless of whether a third party was the first to invent the claimed invention. A third party that files a patent application in the USPTO after March 2013, but before us could therefore be awarded a patent covering an invention of ours even if we had made the invention before it was made by such third party. This will require us to be cognizant going forward of the time from invention to filing of a patent application. Since patent applications in the United States and most other countries are confidential for a period of time after filing or until issuance, we cannot be certain that we were the first to either (i) file any patent application related to our product candidates and other proprietary technologies we may develop or (ii) invent any of the inventions claimed in our patent applications.

The America Invents Act also includes a number of significant changes that affect the way patent applications will be prosecuted and also may affect patent litigation. These include allowing third party submission

of prior art to the USPTO during patent prosecution and additional procedures to attack the validity of a patent by USPTO administered post-grant proceedings, including post-grant review, inter partes review and derivation proceedings. Because of a lower evidentiary standard in USPTO proceedings compared to the evidentiary standard in United States federal courts necessary to invalidate a patent claim, a third party could potentially provide evidence in a USPTO proceeding sufficient for the USPTO to hold a claim invalid even though the same evidence would be insufficient to invalidate the claim if first presented in a district court action. Accordingly, a third party may attempt to use the USPTO procedures to invalidate our patent claims that would not have been invalidated if first challenged by the third party as a defendant in a district court action. Therefore, the America Invents Act and its implementation could increase the uncertainties and costs surrounding the prosecution of our patent applications and the enforcement or defense of patents issuing from those patent applications, all of which could have a material adverse effect on our business, financial condition, results of operations and prospects.

In addition, the patent positions of companies in the development and commercialization of biologics and pharmaceuticals are particularly uncertain. Recent U.S. Supreme Court rulings have narrowed the scope of patent protection available in certain circumstances and weakened the rights of patent owners in certain situations. For example, the scope of patentable subject matter under 35 U.S.C. 101 has evolved significantly over the past several years as the Court of Appeals for the Federal Circuit and the Supreme Court issued various opinions, and the USPTO modified its guidance for practitioners on multiple occasions. This combination of events has created uncertainty with respect to the validity and enforceability of patents, once obtained. Depending on future actions by the U.S. Congress, the federal courts and the USPTO, the laws and regulations governing patents could change in unpredictable ways that could have a material adverse effect on our ability to protect and enforce our intellectual property in the future.

Issued patents relating to our product candidates and other proprietary technologies we may develop could be found invalid or unenforceable if challenged in court or before administrative bodies in the United States or abroad.

If we initiated legal proceedings against a third party to enforce a patent relating to our product candidates and other proprietary technologies we may develop, the defendant could counterclaim that such patent is invalid or unenforceable. In patent litigation in the United States, defendant counterclaims alleging invalidity or unenforceability are commonplace. Grounds for a validity challenge could be an alleged failure to meet any of several statutory requirements, including lack of novelty, obviousness or non-enablement. Grounds for an unenforceability assertion could be an allegation that someone connected with prosecution of the patent withheld relevant information from the USPTO, or made a misleading statement, during prosecution. Third parties may raise claims challenging the validity or enforceability of a patent before administrative bodies in the United States or abroad, even outside the context of litigation. Such mechanisms include re-examination, post-grant review, inter partes review, derivation proceedings, and equivalent proceedings in foreign jurisdictions (e.g., opposition proceedings). Such proceedings could result in the revocation of, cancellation of or amendment to our patents in such a way that they no longer cover our product candidates and other proprietary technologies we may develop. The outcome following legal assertions of invalidity and unenforceability is unpredictable. With respect to the validity question, for example, we cannot be certain that there is no invalidating prior art, of which we or our licensing partners and the patent examiner were unaware during prosecution. If a third party were to prevail on a legal assertion of invalidity or unenforceability, we would lose at least part, and perhaps all, of the patent protection on our product candidates and other proprietary technologies we may develop. Such a loss of patent protection would have a material adverse impact on our business, financial condition, results of operations and prospects.

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

Patents have a limited lifespan. In the United States, if all maintenance fees are timely paid, the natural expiration of a patent is generally 20 years from its earliest U.S. non-provisional filing date. Various extensions may be available, but the life of a patent, and the protection it affords, is limited. Even if patents relating to our product candidates are obtained, once the patent life has expired, we may be open to competition from competitive products. Given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized. As a result, our patent portfolio may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours.

If we do not obtain patent term extension for our product candidates, our business may be materially harmed.

Depending upon the timing, duration and specifics of any FDA marketing approval of any product candidate we may develop, one or more of patents issuing from our U.S. patent applications may be eligible for limited patent term extension under the Drug Price Competition and Patent Term Restoration Action of 1984 (the Hatch-Waxman Amendments). The Hatch-Waxman Amendments permit a patent extension term (PTE) of up to five years as compensation for patent term lost during the FDA regulatory review process. A patent term extension cannot extend the remaining term of a patent beyond a total of 14 years from the date of product approval, only one patent may be extended and only those claims covering the approved drug, a method for using it or a method for manufacturing it may be extended. Similar patent term restoration provisions to compensate for commercialization delay caused by regulatory review are also available in certain foreign jurisdictions, such as in Europe under Supplemental Protection Certificate (SPC). If we encounter delays in our development efforts, including any clinical trials, the period of time during which we could market any future product candidates under patent protection would be reduced. Additionally, we may not receive an extension if we fail to apply within applicable deadlines, fail to apply prior to expiration of relevant patents, or otherwise fail to satisfy applicable requirements. Moreover, the applicable time period or the scope of patent protection afforded could be less than we request. If we are unable to obtain patent term extension or restoration, or the term of any such extension is less than we request, the period during which we will have the right to exclusively market our product will be shortened and our competitors may obtain approval of competing products following our patent expiration, and our revenue could be reduced.

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

We may be subject to claims that former employees, collaborators or other third parties have an interest in our patent rights, trade secrets, or other intellectual property as an inventor or co-inventor. For example, we may have inventorship disputes arise from conflicting obligations of consultants or others who are involved in developing our product candidates and other proprietary technologies we may develop. Litigation may be necessary to defend against these and other claims challenging inventorship or our patent rights, trade secrets or other intellectual property. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights, such as exclusive ownership of, or right to use, intellectual property that is important to our product candidates and other proprietary technologies we may develop. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to our management and other employees. Any of the foregoing could have a material adverse effect on our business, financial condition, results of operations and prospects.

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

In addition to seeking patent protection for our product candidates and other proprietary technologies we may develop, we also rely on trade secrets and confidentiality agreements to protect our unpatented know-how, technology, and other proprietary information and to maintain our competitive position. With respect to our development programs, we consider trade secrets and know-how to be one of our important sources of intellectual property, including our extensive knowledge of crystallography structure-based drug design. Trade secrets and know-how can be difficult to protect. In particular, the trade secrets and know-how in connection with our development programs and other proprietary technology we may develop may over time be disseminated within the industry through independent development, the publication of journal articles describing the methodology and the movement of personnel with scientific positions in academic and industry.

We seek to protect these trade secrets and other proprietary technology, in part, by entering into non-disclosure and confidentiality agreements with parties who have access to them, such as our employees, CROs, consultants, advisors and other third parties. We also enter into confidentiality and invention or patent assignment agreements with our employees and consultants. We cannot guarantee that we have entered into such agreements with each party that may have or have had access to our trade secrets or proprietary technology and processes. Despite these efforts, any of these parties may breach the agreements and disclose our proprietary information, including our trade secrets, and we may not be able to obtain adequate remedies for such breaches. Enforcing a claim that a party illegally disclosed or misappropriated a trade secret is difficult, expensive and time-consuming, and the outcome is unpredictable. In addition, some courts inside and outside the United States are less willing or unwilling to protect trade secrets. If any of our trade secrets were to be lawfully obtained or independently developed by a competitor or other third party, we would have no right to prevent them from using that technology or information to compete with us. If any of our trade secrets were to be disclosed to or independently developed by a competitor or other third party, our competitive position would be materially and adversely harmed.

We may be subject to claims that third parties have an ownership interest in our trade secrets. For example, we may have disputes arise from conflicting obligations of our employees, consultants or others who are involved in developing our product candidate. Litigation may be necessary to defend against these and other claims challenging ownership of our trade secrets. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable trade secret rights, such as exclusive ownership of, or right to use, trade secrets that are important to our product candidates and other proprietary technologies we may develop. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to our management and other employees. We may need to share our proprietary information, including trade secrets, with our current and future business partners, collaborators, contractors and others located in countries at heightened risk of theft of trade secrets, including through direct intrusion by private parties or foreign actors, and those affiliated with or controlled by state actors. Any of the foregoing could have a material adverse effect on our business, financial condition, results of operations and prospects.

We may not be successful in obtaining necessary rights to any product candidate we may develop through acquisitions and in-licenses.

We currently solely own intellectual property rights covering our product candidates. Other pharmaceutical companies and academic institutions may also have filed or are planning to file patent applications potentially relevant to our business. In order to avoid infringing these third-party patents, we may find it necessary or prudent to obtain licenses to such patents from such third-party intellectual property holders. However, we may be unable to secure such licenses or otherwise acquire or in-license any compositions, methods of use, processes or other intellectual property rights from third parties that we identify as necessary for our product candidates and other proprietary technologies we may develop. The licensing or acquisition of third-party intellectual property rights is a

competitive area, and several more established companies may pursue strategies to license or acquire third party intellectual property rights that we may consider attractive or necessary. These established companies may have a competitive advantage over us due to their size, capital resources and greater clinical development and commercialization capabilities. In addition, companies that perceive us to be a competitor may be unwilling to assign or license rights to us. We also may be unable to license or acquire third party intellectual property rights on terms that would allow us to make an appropriate return on our investment or at all. If we are unable to successfully obtain rights to required third party intellectual property rights or maintain the existing intellectual property rights we have, we may have to abandon development of the relevant program or product candidate, which could have a material adverse effect on our business, financial condition, results of operations and prospects.

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

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

In addition, while it is our policy to require our employees and contractors who may be involved in the conception or development of intellectual property to execute agreements assigning such intellectual property to us, we may be unsuccessful in executing such an agreement with each party who, in fact, conceives or develops intellectual property that we regard as our own. The assignment of intellectual property rights may not be self-executing, or the assignment agreements may be breached, and we may be forced to bring claims against third parties, or defend claims that they may bring against us, to determine the ownership of what we regard as our intellectual property. Such claims could have a material adverse effect on our business, financial condition, results of operations and prospects.

Third-party claims of intellectual property infringement, misappropriation or other violations against us or our collaborators may prevent or delay the development and commercialization of our product candidates and other proprietary technologies we may develop.

Our commercial success depends in part on our ability to avoid infringing, misappropriating and otherwise violating the patents and other intellectual property rights of third parties. There is a substantial amount of complex litigation involving patents and other intellectual property rights in the biopharmaceutical and biotechnology industries, as well as administrative proceedings for challenging patents, including derivation and reexamination proceedings before the USPTO or oppositions and other comparable proceedings in foreign jurisdictions. As discussed above, as a result of the America Invests Act, procedures including inter partes review and post-grant review have been implemented. The America Invents Act adds uncertainty to the possibility of challenge to our patents in the future

Numerous U.S. and foreign issued patents and pending patent applications owned by third parties exist in the fields in which we are commercializing or plan to commercialize our product candidates and in which we are developing other proprietary technologies. As the biopharmaceutical and biotechnology industries expand and more patents are issued, the risk increases that our product candidates and commercializing activities may give rise to

claims of infringement of the patent rights of others. We cannot assure you that our product candidates and other proprietary technologies we may develop will not infringe existing or future patents owned by third parties. We may not be aware of patents that have already been issued and that a third party, for example, a competitor in the fields in which we are developing our product candidates, might assert as infringed by us. It is also possible that patents owned by third parties of which we are aware, but which we do not believe we infringe or that we believe we have valid defenses to any claims of patent infringement, could be found to be infringed by us. It is not unusual that corresponding patents issued in different countries have different scopes of coverage, such that in one country a third-party patent does not pose a material risk, but in another country, the corresponding third-party patent may pose a material risk to our planned products. As such, we monitor third-party patents in the relevant pharmaceutical markets. In addition, because patent applications can take many years to issue and may be confidential for 18 months or more after filing, there may be currently pending patent applications that may later result in issued patents that we may infringe.

In the event that any third party claims that we infringe their patents or that we are otherwise employing their proprietary technology without authorization and initiates litigation against us, even if we believe such claims are without merit, a court of competent jurisdiction could hold that such patents are valid, enforceable and infringed by us. In this case, the holders of such patents may be able to block our ability to commercialize the infringing products or technologies unless we obtain a license under the applicable patents, or until such patents expire or are finally determined to be held invalid or unenforceable. Such a license may not be available on commercially reasonable terms or at all. Even if we are able to obtain a license, the license would likely obligate us to pay license fees or royalties or both, and the rights granted to us might be nonexclusive, which could result in our competitors gaining access to the same intellectual property. If we are unable to obtain a necessary license to a third-party patent on commercially reasonable terms, we may be unable to commercialize the infringing products or technologies or such commercialization efforts may be significantly delayed, which could in turn significantly harm our business.

If we collaborate with third parties in the development of technology in the future, our collaborators may not properly maintain or defend our intellectual property rights or may use our proprietary information in such a way as to invite litigation that could jeopardize or invalidate our intellectual property or proprietary information or expose us to litigation or potential liability. Further, collaborators may infringe the intellectual property rights of third parties, which may expose us to litigation and potential liability. In the future, we may agree to indemnify our commercial collaborators against certain intellectual property infringement claims brought by third parties.

Defense of infringement claims, regardless of their merit, would involve substantial litigation expense and would be a substantial diversion of management and other employee resources from our business, and may impact our reputation. In the event of a successful claim of infringement against us, we may be enjoined from further developing or commercializing the infringing products or technologies. In addition, we may have to pay substantial damages, including treble damages and attorneys' fees for willful infringement, obtain one or more licenses from third parties, pay royalties and/or redesign our infringing products or technologies, which may be impossible or require substantial time and monetary expenditure. In that event, we would be unable to further develop and commercialize our product candidate or technologies, which could harm our business significantly. Further, we cannot predict whether any required license would be available at all or whether it would be available on commercially reasonable terms. In the event that we could not obtain a license, we may be unable to further develop our product candidate and commercialize our product, if approved, which could harm our business significantly. Even if we are able to obtain a license, the license would likely obligate us to pay license fees or royalties or both, and the rights granted to us might be nonexclusive, which could result in our competitors gaining access to the same intellectual property. Ultimately, we could be prevented from commercializing a product, or be forced to cease some aspect of our business operations, if, as a result of actual or threatened patent infringement claims, we are unable to enter into licenses on acceptable terms.

Engaging in litigation defending against third parties alleging infringement of patent and other intellectual property rights is very expensive, particularly for a company of our size, and time-consuming. Some of our competitors may be able to sustain the costs of litigation or administrative proceedings more effectively than we can because of greater financial resources. Patent litigation and other proceedings may also absorb significant management time. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could impair our ability to compete in the marketplace. The occurrence of any of the foregoing could have a material adverse effect on our business, financial condition or results of operations.

We may in the future pursue invalidity proceedings with respect to third-party patents. The outcome following legal assertions of invalidity is unpredictable. Even if resolved in our favor, these legal proceedings may cause us to incur significant expenses, and could distract our technical and management personnel from their normal responsibilities. In addition, there could be public announcements of the results of hearings, motions or other interim proceedings or developments and if securities analysts or investors perceive these results to be negative, it could have a substantial adverse effect on the price of our common stock. Such proceedings could substantially increase our operating losses and reduce the resources available for development activities or any future sales, marketing or distribution activities. We may not have sufficient financial or other resources to conduct such proceedings adequately. Some of these third parties may be able to sustain the costs of such proceedings more effectively than we can because of their greater financial resources. If we do not prevail in the patent proceedings the third parties may assert a claim of patent infringement directed at our product candidates.

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

Third parties, such as a competitor, may infringe, misappropriate, or otherwise violate our future issued patents and other intellectual property rights. In a patent infringement proceeding, a court may decide that a patent owned by us is invalid or unenforceable or may refuse to stop the other party from using the invention at issue on the grounds that the patent does not cover the technology in question or that the other party's use of our patented technology falls under the safe harbor to patent infringement under 35 U.S.C. §271(e)(1). In addition, our patent rights may become involved in inventorship, priority or validity disputes. To counter or defend against such claims can be expensive and time consuming. An adverse result in any litigation proceeding could put our patent rights at risk of being invalidated or interpreted narrowly. Furthermore, because of the substantial amount of discovery required in connection with intellectual property litigation, there is a risk that some of our confidential information could be compromised by disclosure during this type of litigation.

Even if resolved in our favor, litigation or other legal proceedings relating to intellectual property claims may cause us to incur significant expenses and could distract our personnel from their normal responsibilities. In addition, there could be public announcements of the results of hearings, motions or other interim proceedings or developments, and if securities analysts or investors perceive these results to be negative, it could have a substantial adverse effect on the price of our common stock. Such litigation or proceedings could substantially increase our operating losses and reduce the resources available for development activities or any future sales, marketing or distribution activities. We may not have sufficient financial or other resources to conduct such litigation or proceedings adequately. Some of our competitors may be able to sustain the costs of such litigation or proceedings more effectively than we can because of their greater financial resources and more mature and developed intellectual property portfolios. Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could have a material adverse effect on our ability to compete in the marketplace.

Our ability to enforce our patent rights depends on our ability to detect infringement. It may be difficult to detect infringers who do not advertise the components or methods that are used in connection with their products and services. Moreover, it may be difficult or impossible to obtain evidence of infringement in a competitor's or

potential competitor's product or service. We may not prevail in any lawsuits that we initiate and the damages or other remedies awarded if we were to prevail may not be commercially meaningful.

Because of the expense and uncertainty of litigation, we may not be in a position to enforce our intellectual property rights against third parties.

Because of the expense and uncertainty of litigation, we may conclude that even if a third party is infringing any patents that may be issued as a result of our pending or future patent applications or other intellectual property rights, the risk-adjusted cost of bringing and enforcing such a claim or action may be too high or not in the best interest of our company or our stockholders. In addition, the uncertainties associated with litigation could compromise our ability to raise the funds necessary to continue any clinical trials, continue our internal research programs, in-license needed technology or other product candidates, or enter into development partnerships that would help us bring our product candidates to market. In such cases, we may decide that the more prudent course of action is to simply monitor the situation or initiate or seek some other non-litigious action or solution.

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

Our registered or unregistered trademarks or trade names may be challenged, infringed, circumvented or declared generic or determined to be infringing on other marks. During trademark registration proceedings, we may receive rejections of our applications by the USPTO or in other foreign jurisdictions. Although we are given an opportunity to respond to those rejections, we may be unable to overcome such rejections. In addition, in the USPTO and in comparable agencies in many foreign jurisdictions, third parties are given an opportunity to oppose pending trademark applications and to seek to cancel registered trademarks. Opposition or cancellation proceedings may be filed against our trademarks, which may not survive such proceedings. Moreover, any name we have proposed to use with our product candidates in the United States must be approved by the FDA, regardless of whether we have registered it, or applied to register it, as a trademark. Similar requirements exist in Europe. The FDA typically conducts a review of proposed product names, including an evaluation of potential for confusion with other product names. If the FDA or an equivalent administrative body in a foreign jurisdiction objects to any of our proposed proprietary product names, we may be required to expend significant additional resources in an effort to identify a suitable substitute name that would qualify under applicable trademark laws, not infringe the existing rights of third parties and be acceptable to the FDA. Furthermore, in many countries, owning and maintaining a trademark registration may not provide an adequate defense against a subsequent infringement claim asserted by the owner of a senior trademark.

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

Intellectual property rights do not necessarily address all potential threats.

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

- others may be able to make products that are similar to our product candidate or utilize similar technology but that are not covered by the claims of the patents that we may license or may own;
- we might not have been the first to make the inventions covered by our current or future patent applications;
- we might not have been the first to file patent applications covering our inventions;
- others may independently develop similar or alternative technologies or duplicate any of our technologies without infringing our intellectual property rights;
- it is possible that our current or future patent applications will not lead to issued patents;
- any patent issuing from our current or future patent applications may be held invalid or unenforceable, including as a result of legal challenges by our competitors or other third parties;
- our competitors or other third parties might conduct research and development activities in countries where we do not have patent rights and then use the information learned from such activities to develop competitive products for sale in our major commercial markets;
- we may not develop additional proprietary technologies that are patentable;
- the patents of others may harm our business; and
- we may choose not to file for patent protection in order to maintain certain trade secrets or know-how, and a third party may subsequently file a patent application covering such intellectual property.

We may not be successful in obtaining or maintaining necessary rights to product components and processes for our development pipeline through acquisitions and in-licenses.

The growth of our business may depend in part on our ability to acquire, in-license or use third-party proprietary component and process rights. For example, our product candidates may require specific formulations to work effectively and efficiently, we may develop product candidates containing our compounds and pre-existing pharmaceutical compounds, or we may be required by the FDA or comparable foreign regulatory authorities to obtain marketing authorization of companion diagnostic test or tests for use with our product candidates, any of which could require us to obtain rights to use intellectual property held by third parties. For example, we plan to work with diagnostic companies to develop and utilize liquid biopsy companion diagnostic tests to aid in identifying appropriate patients in our SURF301 Phase 1/2 clinical trial. In addition, with respect to any patents we may co-own with third parties, we may require licenses to such co-owners interest to such patents. We may be unable to acquire or in-license any compositions, methods of use, processes or other third-party intellectual property rights from third parties that we identify as necessary or important to our business operations. In addition, we may fail to obtain any of these licenses at a reasonable cost or on reasonable terms, if at all. Were that to happen, we may need to cease use of the compositions or methods covered by those third-party intellectual property rights, and may need to seek to develop alternative approaches that do not infringe on those intellectual property rights, which may entail additional costs and development delays, even if we were able to develop such alternatives, which may not be feasible. Even if we are able to obtain a license, it may be non-exclusive, which means that our competitors may also receive access

to the same technologies licensed to us. In that event, we may be required to expend significant time and resources to develop or license replacement technology.

Additionally, we might sometimes collaborate with academic institutions to accelerate our preclinical research or development under written agreements with these institutions. In certain cases, these institutions provide us with an option to negotiate a license to any of the institution's rights in technology resulting from the collaboration. Even if we hold such an option, we may be unable to negotiate a license from the institution within the specified timeframe or under terms that are acceptable to us. If we are unable to do so, the institution may offer the intellectual property rights to others, potentially blocking our ability to pursue our program.

The licensing and acquisition of third-party intellectual property rights is a competitive area, and companies that may be more established or have greater resources than we do may also be pursuing strategies to license or acquire third-party intellectual property rights that we may consider necessary or attractive in order to commercialize our product candidates. More established companies may have a competitive advantage over us due to their size, cash resources and greater clinical development and commercialization capabilities. In addition, companies that perceive us to be a competitor may be unwilling to assign or license rights to us. There can be no assurance that we will be able to successfully complete these types of negotiations and ultimately acquire the rights to the intellectual property surrounding the additional product candidates that we may seek to develop or market. If we are unable to successfully obtain rights to required third-party intellectual property or to maintain the existing intellectual property rights we have, we may have to abandon development of certain programs and our business financial condition, results of operations and prospects could suffer.

Risks Related to Our Common Stock

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

Our stock price is likely to be volatile. The stock market in general and the market for stock of biopharmaceutical companies in particular have experienced extreme volatility that has often been unrelated to the operating performance of particular companies. As a result of this volatility, investors may not be able to sell their common stock at or above the price at which they paid. The market price for our common stock may be influenced by those factors discussed in this "Risk Factors" section and many others, including:

- results of our preclinical studies and clinical trials, and the results of trials of our competitors or those of other companies in our market sector;
- our ability to enroll patients in our future clinical trials;
- marketing approval of our product candidates, or limitations to specific label indications or patient populations for its use, or changes or delays in the regulatory review process;
- regulatory developments in the United States and foreign countries;
- changes in the structure of healthcare payment systems;
- the success or failure of our efforts to develop, acquire or license additional product candidates;
- innovations, clinical trial results, product approvals and other developments regarding our competitors;
- announcements by us or our competitors of significant acquisitions, strategic partnerships, joint ventures or capital commitments;

- manufacturing, supply or distribution delays or shortages;
- any changes to our relationship with any manufacturers, suppliers, collaborators or other strategic partners;
- achievement of expected product sales and profitability;
- variations in our financial results or those of companies that are perceived to be similar to us;
- market conditions in the biopharmaceutical sector and issuance of securities analysts' reports or recommendations;
- trading volume of our common stock;
- an inability to obtain additional funding;
- sales of our stock by insiders and stockholders;
- the impact of any natural disasters or public health emergencies, such as the COVID-19 pandemic;
- general economic, industry, geopolitical and market conditions, events or factors, many of which are beyond our control, such as the COVID-19 pandemic, the military conflict between Russia and Ukraine, inflation and interest rate changes and financial institution instability;
- expiration of market stand-off or lock-up agreements;
- additions or departures of key personnel; and
- intellectual property, product liability or other litigation against us.

In addition, in the past, stockholders have initiated class action lawsuits against biopharmaceutical companies following periods of volatility in the market prices of these companies' stock. Such litigation, if instituted against us, could cause us to incur substantial costs and divert our management's attention and resources, which could have a material adverse effect on our business, financial condition and results of operations.

An active, liquid and orderly market for our common stock may not be maintained.

We can provide no assurance that we will be able to maintain an active trading market for our common stock. If an active market for our common stock is not sustained, it may be difficult for you to sell your shares at the time you wish to sell them or at a price that you consider reasonable. An inactive market may also impair our ability to raise capital by selling shares and may impair our ability to acquire other businesses or technologies using our shares as consideration, which, in turn, could materially adversely affect our business.

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

Our executive officers, directors and greater than 5% stockholders, in the aggregate, own a majority of our outstanding common stock. Furthermore, many of our current directors were appointed by our principal stockholders. As a result, such persons or their appointees to our board of directors, acting together, have the ability to control or significantly influence all matters submitted to our board of directors or stockholders for approval, including the appointment of our management, the election and removal of directors and approval of any significant transaction, as well as our management and business affairs. This concentration of ownership may have the effect of delaying, deferring or preventing a change in control, impeding a merger, consolidation, takeover or other business

combination involving us, or discouraging a potential acquiror from making a tender offer or otherwise attempting to obtain control of our business, even if such a transaction would benefit other stockholders.

We do not currently intend to pay dividends on our common stock, and, consequently, your ability to achieve a return on your investment will depend on appreciation, if any, in the price of our common stock.

We have never declared or paid any cash dividend on our common stock. We currently anticipate that we will retain future earnings for the development, operation and expansion of our business and do not anticipate declaring or paying any cash dividends for the foreseeable future. Any return to stockholders will therefore be limited to the appreciation of their stock. There is no guarantee that shares of our common stock will appreciate in value or even maintain the price at which stockholders have purchased their shares.

Sales of a substantial number of shares of our common stock by our existing stockholders in the public market could cause our stock price to fall.

Sales of a substantial number of shares of our common stock by our executive officers, directors and principal stockholders in the public market or the perception that these sales might occur could significantly reduce the market price of our common stock and impair our ability to raise adequate capital through the sale of additional equity securities.

In addition, the holders of 22,200,527 shares of our outstanding common stock, or approximately 52.1% of our total outstanding common stock based on shares outstanding as of December 31, 2022, will be entitled to rights with respect to the registration of their shares under the Securities Act, subject to vesting. Registration of these shares under the Securities Act would result in the shares becoming freely tradable without restriction under the Securities Act, except for shares held by affiliates, as defined in Rule 144 under the Securities Act. Any sales of securities by these stockholders could have a material adverse effect on the trading price of our common stock.

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

We are an emerging growth company, as defined in the JOBS Act, and may remain an emerging growth company until the last day of the fiscal year following the fifth anniversary of the completion of our IPO. However, if certain events occur prior to the end of such five-year period, including if we become a “large accelerated filer,” our annual gross revenues exceed $1.235 billion or we issue more than $1.0 billion of non-convertible debt in any three-year period, we will cease to be an emerging growth company prior to the end of such five- year period. For so long as we remain an emerging growth company, we are permitted and intend to rely on exemptions from certain disclosure requirements that are applicable to other public companies that are not emerging growth companies. These exemptions include:

- being permitted to provide only two years of audited financial statements, in addition to any required unaudited interim financial statements, with correspondingly reduced “Management’s Discussion and Analysis of Financial Condition and Results of Operations” disclosure;
- not being required to comply with the auditor attestation requirements in the assessment of our internal control over financial reporting pursuant to the Sarbanes-Oxley Act;
- not being required to comply with any requirement that may be adopted by the Public Company Accounting Oversight Board regarding mandatory audit firm rotation or a supplement to the auditor’s report providing additional information about the audit and the financial statements, unless the SEC determines the new rules are necessary for protecting the public;

- reduced disclosure obligations regarding executive compensation; and
- exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and stockholder approval of any golden parachute payments not previously approved.

We cannot predict whether investors will find our common stock less attractive if we rely on these exemptions. If some investors find our common stock less attractive as a result, there may be a less active trading market for our common stock and our stock price may be reduced or more volatile. In addition, the JOBS Act provides that an emerging growth company can take advantage of an extended transition period for complying with new or revised accounting standards. This allows an emerging growth company to delay the adoption of these accounting standards until they would otherwise apply to private companies. We have elected to avail ourselves of this exemption and, therefore, we will not be subject to the same new or revised accounting standards as other public companies that are not emerging growth companies.

We are also a smaller reporting company as defined in the Exchange Act. We may continue to be a smaller reporting company even after we are no longer an emerging growth company. We may take advantage of certain of the scaled disclosures available to smaller reporting companies and will be able to take advantage of these scaled disclosures for so long as our voting and non-voting common stock held by non-affiliates is less than $250.0 million measured on the last business day of our second fiscal quarter, or our annual revenue is less than $100.0 million during the most recently completed fiscal year and our voting and non-voting common stock held by non-affiliates is less than $700.0 million measured on the last business day of our second fiscal quarter.

General Risk Factors

We incur significant costs as a result of operating as a public company, and our management is required to devote substantial time to new compliance initiatives.

As a public company, we incur significant legal, accounting and other expenses. We are subject to the reporting requirements of the Exchange Act, which requires, among other things, that we file with the SEC annual, quarterly and current reports with respect to our business and financial condition. In addition, the Sarbanes-Oxley Act, as well as rules subsequently adopted by the SEC and Nasdaq to implement provisions of Sarbanes-Oxley, impose significant requirements on public companies, including requiring establishment and maintenance of effective disclosure and financial controls and changes in corporate governance practices. Further, pursuant to the Dodd-Frank Wall Street Reform and Consumer Protection Act of 2010, the SEC has adopted additional rules and regulations in these areas, such as mandatory “say on pay” voting requirements and “pay versus performance” disclosure requirements that will apply to us when we cease to be an emerging growth company. Stockholder activism, the current political environment and the current high level of government intervention and regulatory reform may lead to substantial new regulations and disclosure obligations, which may lead to additional compliance costs and impact the manner in which we operate our business in ways we cannot currently anticipate.

The rules and regulations applicable to public companies have substantially increased our legal and financial compliance costs and made some activities more time consuming and costly. If these requirements divert the attention of our management and personnel from other business concerns, they could have a material adverse effect on our business, financial condition and results of operations. The increased costs will decrease our net income or increase our net loss, and may require us to reduce costs in other areas of our business or increase the prices of our products or services. For example, we expect these rules and regulations to make it more difficult and more expensive for us to obtain director and officer liability insurance, and we may be required to incur substantial costs to maintain the same or similar coverage. We cannot predict or estimate the amount or timing of additional costs we may incur to respond to these requirements. The impact of these requirements could also make it more

difficult for us to attract and retain qualified persons to serve on our board of directors, our board committees or as executive officers.

We are subject to U.S. and certain foreign export and import controls, sanctions, embargoes, anti-corruption laws and anti-money laundering laws and regulations. Compliance with these legal standards could impair our ability to compete in domestic and international markets. We could face criminal liability and other serious consequences for violations, which could harm our business.

We are subject to export control and import laws and regulations, including the U.S. Export Administration Regulations, U.S. Customs regulations, and various economic and trade sanctions regulations administered by the U.S. Treasury Department's Office of Foreign Assets Controls and anti-corruption and anti-money laundering laws and regulations, including the U.S. Foreign Corrupt Practices Act of 1977, as amended, the U.S. domestic bribery statute contained in 18 U.S.C. § 201, the U.S. Travel Act, the USA PATRIOT Act and other state and national anti-bribery and anti-money laundering laws in the countries in which we conduct activities. Anti-corruption laws are interpreted broadly and prohibit companies and their employees, agents, CROs, contractors and other collaborators and partners from authorizing, promising, offering, providing, soliciting or receiving, directly or indirectly, improper payments or anything else of value to recipients in the public or private sector. We may engage third parties for clinical trials outside of the United States, to sell our products abroad once we enter a commercialization phase, and/or to obtain necessary permits, licenses, patent registrations and other regulatory approvals. We have direct or indirect interactions with officials and employees of government agencies or government-affiliated hospitals, universities and other organizations. We can be held liable for the corrupt or other illegal activities of our employees, agents, CROs, contractors and other collaborators and partners, even if we do not explicitly authorize or have actual knowledge of such activities. Any violations of the laws and regulations described above may result in substantial civil and criminal fines and penalties, imprisonment, the loss of export or import privileges, debarment, tax reassessments, breach of contract and fraud litigation, reputational harm and other consequences.

Furthermore, U.S. export control laws and economic sanctions prohibit the provision of certain products and services to countries, governments, and persons targeted by U.S. sanctions. U.S. sanctions that have been or may be imposed as a result of military conflicts in other countries may impact our ability to continue activities at future clinical trial sites within regions covered by such sanctions. If we fail to comply with export and import regulations and such economic sanctions, penalties could be imposed, including fines and/or denial of certain export privileges. These export and import controls and economic sanctions could also adversely affect our supply chain.

Business disruptions could seriously harm our future revenue and financial condition and increase our costs and expenses.

Our operations could be subject to earthquakes, power shortages, telecommunications failures, water shortages, floods, hurricanes, typhoons, fires, extreme weather conditions, medical epidemics and other natural or manmade disasters or business interruptions, for which we are predominantly self-insured. We rely on third-party manufacturers to produce our product candidates. Our ability to obtain clinical supplies of our product candidates could be disrupted if the operations of these suppliers were affected by a man-made or natural disaster or other business interruption. In addition, our corporate headquarters is located in Carlsbad, California near major earthquake faults and fire zones, and the ultimate impact on us of being located near major earthquake faults and fire zones and being consolidated in a certain geographical area is unknown. The occurrence of any of these business disruptions could seriously harm our operations and financial condition and increase our costs and expenses.

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

The trading market for our common stock depends in part on the research and reports that securities or industry analysts publish about us, our business, our market or our competitors. If one or more of the analysts who covers us downgrades our stock, our stock price would likely decline. If one or more of these analysts ceases to cover us or fails to regularly publish reports on us, interest in our stock could decrease, which could cause our stock price or trading volume to decline.

If we fail to maintain proper and effective internal control over financial reporting, our ability to produce accurate and timely financial statements could be impaired, investors may lose confidence in our financial reporting and the trading price of our common stock may decline.

Pursuant to Section 404 of the Sarbanes-Oxley Act, our management is required to report upon the effectiveness of our internal control over financial reporting. When we lose our status as an "emerging growth company" and reach an accelerated filer threshold, our independent registered public accounting firm will be required to attest to the effectiveness of our internal control over financial reporting. The rules governing the standards that must be met for our management to assess our internal control over financial reporting are complex and require significant documentation, testing and possible remediation. To comply with the requirements of being a reporting company under the Exchange Act, we may need to upgrade our information technology systems; implement additional financial and management controls, reporting systems and procedures; and hire additional accounting and finance staff. If we or, if required, our independent registered public accounting firm are unable to conclude that our internal control over financial reporting is effective, investors may lose confidence in our financial reporting and the trading price of our common stock may decline.

We cannot assure you that there will not be material weaknesses or significant deficiencies in our internal control over financial reporting in the future. Any failure to maintain internal control over financial reporting could severely inhibit our ability to accurately report our financial condition, results of operations or cash flows. If we are unable to conclude that our internal control over financial reporting is effective, or if our independent registered public accounting firm determines we have a material weakness or significant deficiency in our internal control over financial reporting once that firm begins its Section 404 reviews, investors may lose confidence in the accuracy and completeness of our financial reports, the market price of our common stock could decline, and we could be subject to sanctions or investigations by Nasdaq, the SEC or other regulatory authorities. Failure to remedy any material weakness in our internal control over financial reporting, or to implement or maintain other effective control systems required of public companies, could also restrict our future access to the capital markets.

Provisions in our charter documents and under Delaware law could discourage a takeover that stockholders may consider favorable and may lead to entrenchment of management.

Our amended and restated certificate of incorporation and amended and restated bylaws contain provisions that could significantly reduce the value of our shares to a potential acquiror or delay or prevent changes in control or changes in our management without the consent of our board of directors. The provisions in our charter documents include the following:

- a classified board of directors with three-year staggered terms, which may delay the ability of stockholders to change the membership of a majority of our board of directors;
- no cumulative voting in the election of directors, which limits the ability of minority stockholders to elect director candidates;

- the exclusive right of our board of directors, unless the board of directors grants such right to the stockholders, to elect a director to fill a vacancy created by the expansion of the board of directors or the resignation, death or removal of a director, which prevents stockholders from being able to fill vacancies on our board of directors;

- the required approval of at least 66-2/3% of the shares entitled to vote to remove a director for cause, and the prohibition on removal of directors without cause;

- the ability of our board of directors to authorize the issuance of shares of preferred stock and to determine the price and other terms of those shares, including preferences and voting rights, without stockholder approval, which could be used to significantly dilute the ownership of a hostile acquiror;

- the ability of our board of directors to alter our amended and restated bylaws without obtaining stockholder approval;

- the required approval of at least 66-2/3% of the shares entitled to vote to adopt, amend or repeal our amended and restated bylaws or repeal the provisions of our amended and restated certificate of incorporation regarding the election and removal of directors;

- a prohibition on stockholder action by written consent, which forces stockholder action to be taken at an annual or special meeting of our stockholders;

- an exclusive forum provision providing that the Court of Chancery of the State of Delaware will be the exclusive forum for certain actions and proceedings;

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

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

We are also subject to the anti-takeover provisions contained in Section 203 of the Delaware General Corporation Law. Under Section 203, a corporation may not, in general, engage in a business combination with any holder of 15% or more of its capital stock unless the holder has held the stock for three years or, among other exceptions, the board of directors has approved the transaction.

Our amended and restated certificate of incorporation provides that the Court of Chancery of the State of Delaware will be the exclusive forum for substantially all disputes between us and our stockholders and that the federal district courts shall be the exclusive forum for the resolution of any complaint asserting a cause of action arising under the Securities Act, which could limit our stockholders' ability to obtain a favorable judicial forum for disputes with us or our directors, officers or employees or the underwriters or any offering giving rise to such claim.

Our amended and restated certificate of incorporation provides that the Court of Chancery of the State of Delaware is the exclusive forum for any derivative action or proceeding brought on our behalf, any action asserting a breach of fiduciary duty, any action asserting a claim against us arising pursuant to the Delaware General Corporation Law, our amended and restated certificate of incorporation or our amended and restated bylaws, or any action asserting a claim against us that is governed by the internal affairs doctrine, our amended and restated certificate of incorporation also provides that unless we consent in writing to the selection of an alternative forum, the federal district courts of the United States shall be the exclusive forum for the resolution of any complaint

asserting a cause of action arising under the Securities Act, including all causes of action asserted against any defendant named in such complaint. For the avoidance of doubt, this provision is intended to benefit and may be enforced by us, our officers and directors, the underwriters to any offering giving rise to such complaint, and any other professional entity whose profession gives authority to a statement made by that person or entity and who has prepared or certified any part of the documents underlying the offering. These choice of forum provisions may limit a stockholder's ability to bring a claim in a judicial forum that it finds favorable for disputes with us or our directors, officers or other employees, which may discourage such lawsuits against us and our directors, officers and other employees and result in increased costs for investors to bring a claim. By agreeing to this provision, however, stockholders will not be deemed to have waived our compliance with the federal securities laws and the rules and regulations thereunder. Furthermore, the enforceability of similar choice of forum provisions in other companies' certificates of incorporation has been challenged in legal proceedings, and it is possible that a court could find these types of provisions to be inapplicable or unenforceable. If a court were to find the choice of forum provisions in our amended and restated certificate of incorporation to be inapplicable or unenforceable in an action, we may incur additional costs associated with resolving such action in other jurisdictions, which could adversely affect our business and financial condition.

We could be subject to securities class action litigation.

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

Our disclosure controls and procedures may not prevent or detect all errors or acts of fraud.

We are subject to the periodic reporting requirements of the Exchange Act. We designed our disclosure controls and procedures to reasonably assure that information we must disclose in reports we file or submit under the Exchange Act is accumulated and communicated to management, and recorded, processed, summarized and reported within the time periods specified in the rules and forms of the SEC. We believe that any disclosure controls and procedures or internal controls and procedures, no matter how well-conceived and operated, can provide only reasonable, not absolute, assurance that the objectives of the control system are met.

Item 1B. Unresolved Staff Comments.

None.

Item 2. Properties.

Our corporate headquarters are located in Carlsbad, California, where we lease approximately 4,734 square feet of laboratory and office space (the Current Space). We will be expanding our headquarters with the leasing of approximately 7,377 additional square feet of space in an adjacent building (the Expansion Space). The lease for the Expansion Space will commence when the improvements are complete (estimated to be in the second half of 2023), and will end 120 months thereafter, subject to certain renewal and early termination rights by us. The lease for the Current Space will end 120 months after the commencement date of the Expansion Space lease, subject to certain renewal options granted to us. In no event will the term of the Current Space lease end sooner than 60 months from its original commencement date which would be approximately July 2026. We believe that our existing and planned expansion facilities are adequate for our current needs and that suitable additional or alternative space will be available in the future on commercially reasonable terms, if required.

For additional information, see Note 10, Leases, to the financial statements included in this Annual Report on Form 10-K.

Item 3. Legal Proceedings.

We are not currently subject to any material legal proceedings. From time to time, we may be involved in legal proceedings or subject to claims incident to the ordinary course of business. Regardless of the outcome, such proceedings or claims can have an adverse impact on us because of defense and settlement costs, diversion of resources and other factors, and there can be no assurances that favorable outcomes will be obtained.

Item 4. Mine Safety Disclosures.

Not applicable.

PART II

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

Market Information

Our common stock trades on the Nasdaq Global Select Market under the symbol "TYRA".

Holders of Common Stock

As of March 20, 2023, there were approximately 46 holders of record of our common stock. This number was derived from our shareholder records and does not include beneficial owners of our common stock whose shares are held in the name of various dealers, clearing agencies, banks, brokers and other fiduciaries.

Dividend Policy

We have never declared or paid any cash dividends on our capital stock. We intend to retain future earnings, if any, to finance the operation of our business and do not anticipate paying any cash dividends in the foreseeable future. Any future determination related to dividend policy will be made at the discretion of our board of directors after considering our financial condition, results of operations, capital requirements, business prospects and other factors the board of directors deems relevant, and subject to the restrictions contained in any future financing instruments.

Securities Authorized for Issuance Under Equity Compensation Plans

See Item 12 of Part III of this Annual Report for information about our equity compensation plans which is incorporated by reference herein.

Performance Graph

Not applicable.

Unregistered Sales of Equity Securities

None.

Use of Proceeds

On September 14, 2021, our registration statement on Form S-1 (File No. 333-258970) was declared effective by the SEC for our IPO. At the closing of the offering on September 17, 2021, we sold 12,420,000 shares of common stock, which included the exercise in full by the underwriters of their option to purchase 1,620,000 additional shares, at an initial public offering price of $16.00 per share and received gross proceeds of $198.7 million, which resulted in net proceeds to us of approximately $181.2 million, after deducting underwriting

discounts and commissions of approximately $13.9 million and offering-related transaction costs of approximately $3.6 million. None of the expenses associated with the IPO were paid to directors, officers, persons owning 10% or more of any class of equity securities, or to their associates, or to our affiliates. BofA Securities, Inc., Jefferies LLC, and Cowen and Company, LLC acted as joint book-running managers for the offering.

As of December 31, 2022, we estimate that we have used approximately $61.5 million of the proceeds from our IPO for general corporate purposes, including to fund the development of TYRA-300, TYRA-200 and our other development programs. There has been no material change in the planned use of proceeds from that described in the final prospectus filed with the SEC pursuant to Rule 424(b)(4) under the Securities Act on September 15, 2021.

Issuer Repurchases of Equity Securities and Affiliated Purchasers

None.

Item 6. [Reserved].

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

You should read the following discussion and analysis of our financial condition and results of operations together with our financial statements and related notes included elsewhere in this Annual Report on Form 10-K. This discussion contains forward-looking statements that involve risks and uncertainties, including those described in the section entitled "Forward Looking Statements and Market Data." Our actual results and the timing of selected events could differ materially from those discussed below. Factors that could cause or contribute to such differences include, but are not limited to, those identified below and those set forth under the section entitled "Risk Factors" or in other parts of this Annual Report.

Overview

We are a clinical-stage biotechnology company focused on developing next-generation precision medicines that target large opportunities in Fibroblast Growth Factor Receptor (FGFR) biology. Our in-house precision medicine platform, SNÅP, enables rapid and precise drug design through iterative molecular SNÅPshots that help predict genetic alterations most likely to cause acquired resistance to existing therapies. Our initial focus is on applying our accelerated small molecule drug discovery engine to develop therapies in targeted oncology and genetically defined conditions.

In oncology, the widespread availability of approved targeted treatments, such as kinase inhibitors, has transformed the cancer treatment landscape. Despite the therapeutic benefit that targeted oncology treatments have created for some patients, the response rate and duration of efficacy is often limited by acquired drug resistance, off-target toxicities and other shortcomings of existing therapies. We are using our proprietary SNÅP platform, which is optimized to enable rapid and precise refinement of structural design through iterative molecular SNÅPshots, in order to generate novel product candidates that are specifically designed to limit off-target toxicities and address acquired drug resistance to provide next-generation treatment options. Genomic alterations in FGFR family members occur in approximately 7% of all human cancers, representing about 126,000 new cases per year.

We are advancing multiple oncology product candidates toward the clinic, including our lead product candidate TYRA-300, an FGFR3 selective inhibitor with an initial focus on patients with metastatic urothelial carcinoma of the bladder and urinary tract (mUC). We submitted an Investigational New Drug application (IND) to the U.S. Food and Drug Administration (FDA) for TYRA-300 in June 2022 and received clearance in July 2022 to proceed with our Phase 1/2 clinical trial of TYRA-300, SURF301 (**S**tudy in **U**ntreated and **R**esistant **F**GFR3+ Advanced Solid Tumors), a multi-center, open label study designed to determine the optimal and maximum tolerated doses and the recommended Phase 2 dose of TYRA-300, as well as to evaluate the preliminary antitumor activity of TYRA-300. In November 2022, the first patient was dosed with TYRA-300 in our Phase 1/2 study SURF301.

Beyond oncology, FGFR3 is implicated in many developmental conditions, such as achondroplasia (ACH) and other skeletal dysplasias, due to its role in regulating bone and cartilage formation. In March 2023, we announced we were expanding development of TYRA-300 into achondroplasia (ACH) based on positive preclinical results demonstrated in a study performed in collaboration with the Imagine Institute in Paris, France. Achondroplasia, the most common form of dwarfism, is a skeletal dysplasia in which growth plate cartilage is affected, resulting in decreased growth of the long bones, vertebral bodies and skull base. These growth differences can result in health complications such as cranial and spinal stenosis, hydrocephalus, genu varum (bowed legs), and sleep apnea. A specific mutation in FGFR3 causes an estimated 97% of achondroplasia. We believe that the design of TYRA-300 may have a meaningful impact on achondroplasia and other skeletal dysplasias. We are planning additional IND-enabling studies and anticipate submitting an IND to the FDA to enable a Phase 2 study in pediatric achondroplasia in 2024.

We are also advancing our second oncology product candidate, TYRA-200, an FGFR1/2/3 inhibitor with potency against activating FGFR2 gene alterations, as well as clinically important molecular brake and gatekeeper resistance mutations. In December 2022, we submitted an IND to the FDA for TYRA-200 and received clearance in January 2023 to proceed with a Phase 1 clinical trial of TYRA-200, which will be focused on intrahepatic cholangiocarcinoma resistant to other FGFR inhibitors. We anticipate dosing the first patient in this trial in the second half of 2023.

Since the commencement of our operations in 2018, we have devoted substantially all of our resources to organizing and staffing the company, business planning, raising capital, developing our proprietary SNÅP platform, undertaking research and development activities for our development programs, establishing our intellectual property portfolio, and providing general and administrative support for our operations. We have not generated any revenue to date and have funded our operations primarily from our initial public offering (IPO), private placements of our convertible preferred stock, and the issuance of Simple Agreements for Future Equity. Our net losses for the years ended December 31, 2022 and 2021 were $55.3 million and $26.3 million, respectively. As of December 31, 2022, we had an accumulated deficit of $95.7 million. As of December 31, 2022, we had cash and cash equivalents of $251.2 million.

We have incurred significant operating losses since inception. Our net losses may fluctuate significantly from quarter-to-quarter and year-to-year, depending on the timing of our clinical development activities, other research and development activities and capital expenditures. We expect to continue to incur significant expenses and increasing operating losses for the foreseeable future particularly if and as we conduct preclinical studies and clinical trials, continue our research and development activities, utilize third parties to manufacture our product candidates and related raw materials, hire additional personnel, expand and protect our intellectual property, and incur additional costs associated with being a public company.

Based on our current operating plan, we believe that our existing cash and cash equivalents will be sufficient to fund our operating expenses and capital expenditures through at least 2024. We have never generated any revenue and do not expect to generate any revenues from product sales unless and until we successfully complete development of and obtain regulatory approval for our product candidates, which will not be for several years, if ever. In addition, if we obtain regulatory approval for any of our product candidates, we expect to incur significant commercialization expenses related to product sales, marketing, manufacturing and distribution. Accordingly, until such time as we can generate significant revenue from sales of our product candidates, if ever, we expect to finance our cash needs through equity offerings, debt financings or other capital sources, including potential collaborations, licenses and other similar arrangements. However, we may not be able to raise additional funds or enter into such other arrangements when needed or on favorable terms, or at all. If we are unable to raise additional capital or enter into such arrangements when needed, we could be forced to delay, limit, reduce or terminate our research and development programs or future commercialization efforts, or grant rights to develop and market our product candidates even if we would otherwise prefer to develop and market such product candidates ourselves.

Components of Results of Operations

Operating Expenses

Research and Development Expenses

To date, our research and development expenses consist primarily of external and internal costs related to the development of our SNÅP platform and our product candidates and development programs. Our research and development expenses primarily include:

- external costs, including:
    - expenses incurred in connection with conducting clinical trials, including investigator grants and site payments for time and pass-through expenses and expenses incurred under agreements with CROs, central laboratories and other vendors and service providers engaged to conduct our trials;
    - expenses incurred in connection with the discovery and preclinical development of our product candidates, including under agreements with third parties, such as consultants and CROs;
    - costs associated with consultants for chemistry, manufacturing and controls (CMC) development, and other services;

- the cost of manufacturing compounds for use in our preclinical studies, including under agreements with third parties, such as consultants and third-party manufacturers; and
- costs related to compliance with drug development regulatory requirements; and

- internal costs, including:
  - employee-related expenses, including salaries, related benefits, travel and share-based compensation expenses for employees engaged in research and development functions;
  - the costs of laboratory supplies and acquiring, developing and manufacturing preclinical study materials; and
  - facilities, depreciation and other expenses, which include allocated expenses for rent and maintenance of facilities, and supplies.

We expense research and development expenses in the periods in which they are incurred. External expenses are recognized based on an evaluation of the progress to completion of specific tasks using information provided to us by our service providers or our estimate of the level of service that has been performed at each reporting date. We track external expenses on a development program and other program specific basis. However, we do not track internal costs on a program specific basis because these costs primarily relate to compensation, early research and consumable costs, which are deployed across multiple programs under development.

Research and development activities are central to our business model. There are numerous factors associated with the successful development of any of our product candidates, including future trial design and various regulatory requirements, many of which cannot be determined with accuracy at this time based on our stage of development. In addition, future regulatory factors beyond our control may impact our clinical development programs. Product candidates in later stages of development generally have higher development costs than those in earlier stages of development. As a result, we expect that our research and development expenses will increase substantially over the next several years as we advance our product candidates through preclinical studies into and through clinical trials, continue to discover and develop additional product candidates and expand our pipeline, maintain, expand, protect and enforce our intellectual property portfolio, and hire additional personnel.

Our future research and development expenses may vary significantly based on a wide variety of factors such as:

- the number and scope, rate of progress, expense and results of our discovery and preclinical development activities and clinical trials;
- the number of trials required for approval;
- the number of sites included in each of our trials;
- the countries in which the trials are conducted;
- the length of time required to enroll eligible patients;
- the number of patients that participate in the trials;
- the ability to identify appropriate patients eligible for our clinical trials;
- the number of doses that patients receive;
- the drop-out or discontinuation rates of patients;
- potential additional safety monitoring requested by regulatory agencies;

- the duration of patient participation in the trials and follow-up;
- the phase of development of the product candidate;
- the efficacy and safety profile of the product candidate;
- the timing, receipt, and terms of any approvals from applicable regulatory authorities including the FDA and non-U.S. regulators;
- maintaining a continued acceptable safety profile of our product candidates following approval, if any;
- the cost and timing of manufacturing our product candidates;
- significant and changing government regulation and regulatory guidance;
- the impact of any business interruptions to our operations or to those of the third parties with whom we work, particularly in light of the COVID-19 pandemic environment;
- geopolitical instability, such as the war in Ukraine;
- adverse effects on the financial markets, the global economy, the supply chain and our expenses due to the COVID-19 pandemic or other epidemic diseases, geopolitical instability, inflation, rising interest rates and other factors; and
- the extent to which we establish additional strategic collaborations or other arrangements.

A change in the outcome of any of these variables with respect to the development of any of our product candidates could significantly change the costs and timing associated with the development of that product candidate.

The process of conducting the necessary preclinical and clinical research to obtain regulatory approval is costly and time-consuming. The actual probability of success for our product candidates or any future candidates may be affected by a variety of factors. We may never succeed in achieving regulatory approval for any of our product candidates or any future candidates.

General and Administrative Expenses

General and administrative expenses consist primarily of personnel-related expenses, including employee salaries, bonuses, benefits, and stock-based compensation charges, for personnel in executive and administrative functions. Other significant general and administrative expenses include legal fees relating to intellectual property and corporate matters, professional fees for accounting, tax and consulting services and insurance costs. We expect our general and administrative expenses will increase for the foreseeable future to support our increased research and development activities, manufacturing activities, and the increased costs associated with operating as a public company. These increased costs will likely include increased expenses related to hiring of additional personnel, audit, legal, regulatory and tax-related services associated with maintaining compliance with exchange listing and SEC requirements, director and officer insurance costs, and investor and public relations costs.

Results of Operations for the Years Ended December 31, 2022 and 2021

The following table summarizes our results of operations for the periods indicated (in thousands):

	Year Ended December 31,		
	2022	2021	Change
Operating expenses:			
Research and development	$ 43,008	$ 20,636	$ 22,372
General and administrative	15,919	5,652	10,267
Total operating expenses	58,927	26,288	32,639
Loss from operations	(58,927)	(26,288)	(32,639)
Other income (expense):			
Interest income	3,652	13	3,639
Other expense	(50)	(19)	(31)
Total other income (expense)	3,602	(6)	3,608
Net loss and comprehensive loss	$ (55,325)	$ (26,294)	$ (29,031)

Research and Development Expenses

Research and development expenses were $43.0 million and $20.6 million for the years ended December 31, 2022 and 2021, respectively. The increase of $22.4 million was primarily due to additional spend to support the advancement of TYRA-300 and TYRA-200 and the enhancement of our SNÅP platform, including $15.1 million of expenses incurred in connection with clinical trials, preclinical and discovery studies, and $7.3 million of higher personnel-related costs, including $3.6 million of non-cash stock-based compensation costs.

The following table summarizes our research and development expenses by development program for the years ended December 31, 2022 and 2021 (in thousands):

	Year Ended December 31,	
	2022	2021
External research and development expense by program		
TYRA-300	$ 9,958	$ 5,964
TYRA-200	5,879	2,593
FGFR3 ACH	2,676	895
RET	4,936	2,882
FGFR4	1,988	1,509
Other development programs	2,086	54
Unallocated research and development expense		
Other research and development	2,822	1,391
Compensation and stock-based compensation	12,663	5,348
Total research and development expense	$ 43,008	$ 20,636

General and Administrative Expenses

General and administrative expenses were $15.9 million and $5.7 million for the years ended December 31, 2022 and 2021, respectively. The increase of $10.2 million was primarily due to increases of $6.5 million in personnel-related expenses, including $4.1 million in non-cash stock-based compensation costs, $1.8 million in professional services related to legal, accounting services, and other consulting fees and $1.9 million in other operating expenses.

Liquidity and Capital Resources

Sources of Liquidity

On September 17, 2021, we completed our IPO and issued 12,420,000 shares of common stock for net proceeds of approximately $181.2 million. Prior to our initial public offering, we funded our operations primarily through private placements of our convertible preferred stock with net proceeds of $157.2 million excluding issuance costs of $0.4 million.

Our primary uses of cash to date have been to fund our research and development activities, including with respect to TYRA-300 and TYRA-200 and other research programs, business planning, establishing and maintaining our intellectual property portfolio, hiring personnel, raising capital, and providing general and administrative support for these operations.

On October 3, 2022, we entered into an ATM Sales Agreement (the Sales Agreement) with Virtu Americas LLC (the Agent), under which we may, from time to time, sell shares of our common stock having an aggregate offering price of up to $150.0 million in "at the market" offerings through the Agent. Sales of the shares of common stock, if any, will be made at prevailing market prices at the time of sale, or as otherwise agreed with the Agent. The Agent will receive a commission from us of up to 3.0% of the gross proceeds of any shares of common stock sold under the Sales Agreement.

We are not obligated to sell, and the Agent is not obligated to buy or sell, any shares of common stock under the Sales Agreement. No assurance can be given that we will sell any shares of common stock under the Sales Agreement, or, if we do, as to the price or amount of shares of common stock that we may sell or the dates when such sales will take place.

Cash Flows

The following table sets forth a summary of our cash flows for the periods indicated (in thousands):

	Year Ended December 31,	
	2022	2021
Net cash used in operating activities	$ (50,285)	$ (23,745)
Net cash used in investing activities	(559)	(645)
Net cash provided by financing activities	632	311,348
Net cash increase (decrease) for the period	$ (50,212)	$ 286,958

Operating Activities

Net cash used in operating activities for the year ended December 31, 2022 was $50.3 million, consisting primarily of our net loss of $55.3 million, adjusted for $10.9 million of non-cash charges primarily related to stock-based compensation expense and $5.9 million for net changes in operating assets and liabilities primarily related to increases in prepaid expenses and other assets of $8.3 million, partially offset by increases in accounts payable and accrued liabilities and other liabilities of $2.4 million.

Net cash used in operating activities for the year ended December 31, 2021 was $23.7 million, consisting primarily of our net loss of $26.3 million, adjusted for $3.0 million of non-cash charges primarily related to stock-based compensation expense and $0.4 million for net changes in operating assets and liabilities primarily related to increases in prepaid expenses and other assets of $2.1 million, partially offset by increases in accounts payable and accrued liabilities and other liabilities of $1.7 million.

Investing Activities

Net cash used in investing activities for the years ended December 31, 2022 and 2021 was $0.6 million and $0.6 million, respectively, consisting of purchases of property and equipment.

Financing Activities

Net cash provided by financing activities was $0.6 million for the year ended December 31, 2022 and was primarily related to proceeds from issuances of common stock under benefit plans.

Net cash provided by financing activities was $311.3 million for the year ended December 31, 2021 and was primarily related to net proceeds of $181.2 million from our IPO, net of issuance costs, in addition to net proceeds of $23.5 million from the second closing of our Series A convertible preferred stock financing, $106.1 million in net proceeds from the issuance of our Series B convertible preferred stock, and $0.5 million from proceeds from issuances of common stock under benefit plans.

Future Funding Requirements

Based on our current operating plan, we believe that our existing cash and cash equivalents will be sufficient to meet our anticipated operating expenses and capital expenditures through at least 2024. However, our forecast of the period of time through which our financial resources will be adequate to support our operations is a forward-looking statement that involves risks and uncertainties, and actual results could vary materially. We have based this estimate on assumptions that may prove to be wrong, and we could deplete our capital resources sooner than we expect. Additionally, the process of conducting preclinical studies and testing product candidates in clinical trials is costly, and the timing of progress and expenses in these studies and trials is uncertain.

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

- the initiation, type, number, scope, results, costs and timing of, our ongoing and planned preclinical studies and clinical trials of existing product candidates or clinical trials of other potential product candidates we may choose to pursue in the future, including based on feedback received from regulatory authorities;
- the costs and timing of manufacturing for current or future product candidates, including commercial scale manufacturing if any product candidate is approved;
- the costs, timing and outcome of regulatory review of current or future product candidates;
- the costs of obtaining, maintaining and enforcing our patents and other intellectual property rights;
- our efforts to enhance operational systems and hire additional personnel to satisfy our obligations as a public company, including enhanced internal controls over financial reporting;
- the costs associated with hiring additional personnel and consultants as our business grows, including additional executive officers and clinical development personnel;
- the costs and timing of establishing or securing sales and marketing capabilities if any current or future product candidate is approved;
- our ability to achieve sufficient market acceptance, coverage and adequate reimbursement from third-party payors and adequate market share and revenue for any approved products;
- costs associated with any products or technologies that we may in-license or acquire; and
- delays or issues with any of the above, including that the risk of each may be exacerbated by the ongoing COVID-19 pandemic, any future epidemic diseases, potential geopolitical instability, inflation or rising interest rates.

Until such time, if ever, as we can generate substantial product revenues to support our cost structure, we expect to finance our cash needs through equity offerings, debt financings or other capital sources, including potential collaborations, licenses and other similar arrangements. However, we may be unable to raise additional

funds or enter into such other arrangements when needed on favorable terms or at all. To the extent that we raise additional capital through the sale of equity or convertible debt securities, the ownership interest of our stockholders could be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect the rights of our common stockholders. Debt financing and equity financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends. If we raise funds through collaborations, or other similar arrangements with third parties, we may have to relinquish valuable rights to our technologies, future revenue streams, research programs or product candidates or grant licenses on terms that may not be favorable to us and/or may reduce the value of our common stock. If we are unable to raise additional funds through equity or debt financings when needed, we may be required to delay, limit, reduce or terminate our product development or future commercialization efforts or grant rights to develop and market our product candidates even if we would otherwise prefer to develop and market such product candidates ourselves.

Contractual Obligations and Commitments

We lease our corporate office and laboratory space in Carlsbad, California (the Original Lease).

In March 2022, we entered into an agreement (the Expansion Lease), for additional office and laboratory space. The Expansion Lease is expected to commence in the second half of 2023 and projected lease payments over the life of the lease are expected to be $5.5 million with a lease expiration of 120 months after the commencement of the Expansion Lease. Additionally, in March 2022, the Original Lease was amended to extend the lease term to 120 months, which will be coterminous with the Expansion Lease after its commencement. The Company has an option to renew the Expansion Lease and the Original Lease for two thirty-six month periods. As of December 31, 2022, total future aggregate operating lease commitments was $9.1 million, with approximately $0.5 million due in 2023, and the remaining due in periods from 2024 through 2033. These obligations are further described in Note 10 to our audited financial statements.

In addition, we have entered into agreements in the normal course of business with certain vendors for the provision of goods and services, which includes manufacturing services with CMOs and development services with CROs. These agreements may include certain provisions for purchase obligations and termination obligations that could require payments for the cancellation of committed purchase obligations or for early termination of the agreements. The amount of the cancellation or termination payments vary and are based on the timing of the cancellation or termination and the specific terms of the agreement. These obligations and commitments are not separately presented.

Critical Accounting Policies, Significant Judgments, and Use of Estimates

Our management's discussion and analysis of our financial condition and results of operations are based on our financial statements, which have been prepared in accordance with GAAP. The preparation of these financial statements requires us to make estimates and judgments that affect the reported amounts of assets, liabilities, revenue and expenses and the disclosure of contingent assets and liabilities in our financial statements. We base our estimates on historical experience, known trends and events, and on various other factors that we believe are reasonable under the circumstances, the results of which form the basis for making judgments about the carrying values of assets and liabilities that are not readily apparent from other sources. Our actual results may differ from these estimates under different assumptions or conditions.

While our significant accounting policies are described in more detail in Note 2 to our financial statements included elsewhere in this filing, we believe the following accounting policies and estimates to be most critical to the preparation of our financial statements.

Accrued Research and Development Expense

Research and development expenses consist of external and internal costs associated with the Company's research and development activities, including its discovery and research efforts and the preclinical and clinical development of its product candidates. Research and development costs are expensed in the period incurred.

The Company has entered into various research and development contracts with clinical research organizations, clinical manufacturing organizations, clinical sites and other vendors and consultants. Payments for these activities are based on the terms of the individual agreements, which may differ from the pattern of costs incurred, and payments made in advance of or after performance are reflected in the accompanying balance sheets as prepaid expenses or accrued liabilities, respectively. The Company records accruals for estimated costs incurred for ongoing research and development activities. When evaluating the adequacy of the accrued liabilities, the Company analyzes progress of the services, including the phase or completion of events, invoices received and contracted costs. The Company holds discussions with applicable personnel and outside service providers as to the progress of clinical trials, or the services completed. Significant judgments and estimates may be made in determining the prepaid or accrued balances at the end of any reporting period. Actual results could differ from the Company's estimates. Nonrefundable advance payments for goods and services, including fees for process development, are deferred and recognized as expense in the period that the related goods are consumed, or services are performed.

Recently Issued Accounting Pronouncements

A description of recently issued accounting pronouncements that may potentially impact our financial position and results of operations is disclosed in Note 2 to our financial statements appearing elsewhere in this Annual Report on Form 10-K.

Emerging Growth Company and Smaller Reporting Company Status

We are an "emerging growth company" as defined in the Jumpstart Our Business Startups Act of 2012, as amended (JOBS Act). We will remain an emerging growth company until the earliest to occur of: (i) the last day of the fiscal year in which we have more than $1.235 billion in annual revenue; (ii) the date we qualify as a "large accelerated filer," with at least $700 million of equity securities held by non-affiliates; (iii) the date on which we have issued more than $1.0 billion in non-convertible debt securities during the prior three-year period; and (iv) December 31, 2026. As a result of this status, we have taken advantage of reduced reporting requirements in this Annual Report on Form 10-K and may elect to take advantage of other reduced reporting requirements in our future filings with the SEC. In particular, in this Annual Report on Form 10-K, we have provided only two years of audited financial statements and have not included all of the executive compensation related information that would be required if we were not an emerging growth company.

In addition, the JOBS Act provides that an emerging growth company can take advantage of an extended transition period for complying with new or revised accounting standards, delaying the adoption of these accounting standards until they would apply to private companies. We have elected to use the extended transition period to enable us to comply with new or revised accounting standards that have different effective dates for public and private companies until the earlier of the date on which we (i) are no longer an emerging growth company and (ii) affirmatively and irrevocably opt out of the extended transition period provided in the JOBS Act. As a result, our financial statements may not be comparable to companies that comply with new or revised accounting pronouncements as of public company effective dates.

We are also a "smaller reporting company" as defined in the Exchange Act. We may continue to be a smaller reporting company if either (i) the market value of our stock held by non-affiliates is less than $250 million measured on the last business day of our second fiscal quarter or (ii) our annual revenue was less than $100 million during the most recently completed fiscal year and the market value of our stock held by non-affiliates is less than $700 million measured on the last business day of our second fiscal quarter. If we are a smaller reporting company at the time we cease to be an emerging growth company, we may continue to rely on exemptions from certain disclosure requirements that are available to smaller reporting companies. Specifically, as a smaller reporting company we may choose to present only the two most recent fiscal years of audited financial statements in our Annual Report on Form 10-K and, similar to emerging growth companies, smaller reporting companies have reduced disclosure obligations regarding executive compensation and other matters.

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

Interest Rate Risk

Our cash and cash equivalents consist of cash in readily available checking accounts and money market funds. As a result, the fair value of our portfolio is relatively insensitive to interest rate changes.

Foreign Currency Exchange Risk

Our expenses are generally denominated in U.S. dollars. However, we have entered into a limited number of contracts with vendors for research and development services that are denominated in foreign currencies. We are subject to foreign currency transaction gains or losses on our contracts denominated in foreign currencies. As of December 31, 2022, foreign currency transaction gains and losses have not been material to our financial statements, and we have not had a formal hedging program with respect to foreign currency. A hypothetical 10% increase or decrease in exchange rates during any of the periods presented would not have had a material impact on our financial results.

Effects of Inflation

Inflation generally affects us by increasing our cost of labor and clinical trial costs. We do not believe that inflation has had a material effect on our financial results during the periods presented.

Item 8. Financial Statements and Supplementary Data.

Report of Independent Registered Public Accounting Firm

To the Stockholders and the Board of Directors of Tyra Biosciences, Inc.

Opinion on the Financial Statements

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

Basis for Opinion

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

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

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

/s/ Ernst & Young LLP

We have served as the Company's auditor since 2021.

San Diego, California
March 22, 2023

Tyra Biosciences, Inc.
Balance Sheets
(in thousands, except share and par value data)

	December 31, 2022	December 31, 2021
Assets		
Current assets:		
Cash and cash equivalents	$ 251,213	$ 302,182
Prepaid and other current assets	6,075	1,875
Total current assets	257,288	304,057
Restricted cash	1,000	243
Property and equipment, net	1,077	1,027
Right-of-use asset	2,466	1,062
Other long-term assets	4,350	312
Total assets	$ 266,181	$ 306,701
Liabilities and Stockholders' Equity		
Current liabilities:		
Accounts payable (including related party amounts of $0 and $47, respectively)	$ 1,145	$ 599
Lease liabilities, current	140	202
Accrued and other current liabilities (including related party amounts of $59 and $0, respectively)	4,416	2,815
Total current liabilities	5,701	3,616
Lease liabilities, noncurrent	2,482	981
Other long-term liabilities	169	367
Total liabilities	8,352	4,964
Commitments and contingencies (Note 11)		
Stockholders' equity:		
Preferred stock, $0.0001 par value; 50,000,000 shares authorized at December 31, 2022 and December 31, 2021; no shares issued and outstanding at December 31, 2022 and December 31, 2021.	—	—
Common stock, $0.0001 par value; 500,000,000 shares authorized at December 31, 2022 and 2021; 42,634,459 and 42,536,183 shares issued at December 31, 2022 and December 31, 2021, respectively, and 42,353,550 and 41,441,135 shares outstanding at December 31, 2022 and December 31, 2021, respectively.	4	4
Additional paid-in capital	353,521	342,104
Accumulated deficit	(95,696)	(40,371)
Total stockholders' equity	257,829	301,737
Total liabilities and stockholders' equity	$ 266,181	$ 306,701

See accompanying notes to financial statements.

Tyra Biosciences, Inc.
Statements of Operations and Comprehensive Loss
(in thousands, except share and per share data)

	Year Ended December 31,	
	2022	2021
Operating expenses:		
Research and development	$ 43,008	$ 20,636
General and administrative (including related party amounts of $765 and $435, respectively)	15,919	5,652
Total operating expenses	58,927	26,288
Loss from operations	(58,927)	(26,288)
Other income (expense):		
Interest income	3,652	13
Other expense	(50)	(19)
Total other income (expense)	3,602	(6)
Net loss and comprehensive loss	$ (55,325)	$ (26,294)
Net loss per share, basic and diluted	$ (1.32)	$ (1.91)
Weighted-average shares used to compute net loss per share, basic and diluted	41,883,904	13,780,546

See accompanying notes to financial statements.

Tyra Biosciences, Inc.
Statements of Convertible Preferred Stock and Stockholders' Equity (Deficit)
(in thousands, except share amounts)

	Series A Convertible Preferred Stock		Series B Convertible Preferred Stock		Common Stock		Additional Paid-In Capital	Accumulated Deficit	Total Stockholders' Equity (Deficit)
	Shares	Amount	Shares	Amount	Shares	Amount			
Balance at December 31, 2020	3,374,560	$ 27,651	—	$ —	1,829,377	$ —	$ 439	$ (14,077)	$ (13,638)
Issuance of Series A convertible preferred stock, net of issuance costs	2,848,486	23,495	—	—	—	—	—	—	—
Issuance of Series B convertible preferred stock, net of issuance costs	—	—	3,874,793	106,128	—	—	—	—	—
Preferred stock converted into shares of common stock	(6,223,046)	(51,146)	(3,874,793)	(106,128)	26,228,089	3	157,271	—	157,274
Initial public offering of common shares, net of issuance costs	—	—	—	—	12,420,000	1	181,219	—	181,220
Issuance of common stock under benefit plans	—	—	—	—	141,767	—	89	—	89
Vesting of shares of common stock subject to repurchase	—	—	—	—	821,902	—	199	—	199
Stock-based compensation	—	—	—	—	—	—	2,887	—	2,887
Net loss	—	—	—	—	—	—	—	(26,294)	(26,294)
Balance at December 31, 2021	—	$ —	—	$ —	41,441,135	$ 4	$ 342,104	$ (40,371)	$ 301,737
Issuance of common stock under benefit plans	—	—	—	—	98,276	—	632	—	632
Vesting of shares of common stock subject to repurchase	—	—	—	—	814,139	—	197	—	197
Stock-based compensation	—	—	—	—	—	—	10,588	—	10,588
Net loss	—	—	—	—	—	—	—	(55,325)	(55,325)
Balance at December 31, 2022	—	$ —	—	$ —	42,353,550	$ 4	$ 353,521	$ (95,696)	$ 257,829

See accompanying notes to financial statements.

Tyra Biosciences, Inc.
Statements of Cash Flows
(in thousands)

	Year Ended December 31,	
	2022	2021
Cash flows from operating activities:		
Net loss	$ (55,325)	$ (26,294)
Adjustments to reconcile net loss to net cash used in operating activities:		
Depreciation and amortization	296	140
Stock-based compensation	10,588	2,887
Loss on disposal of property and equipment	3	3
Changes in operating assets and liabilities:		
Prepaid expenses and other assets	(8,238)	(2,108)
Accounts payable, accrued expenses and other liabilities (including related party amounts of $12 and $47, respectively)	2,357	1,492
Right-of-use assets and lease liabilities, net	34	135
Net cash used in operating activities	(50,285)	(23,745)
Cash flows from investing activities:		
Purchases of property and equipment	(559)	(661)
Proceeds from sale of property and equipment	—	16
Net cash used in investing activities	(559)	(645)
Cash flows from financing activities:		
Proceeds from initial public offering, net of issuance costs	—	181,220
Proceeds from the issuance of Series A convertible preferred stock, net of issuance costs	—	23,495
Proceeds from the issuance of Series B convertible preferred stock, net of issuance costs	—	106,128
Proceeds from issuances of common stock under benefit plans	632	514
Payments for financing lease	—	(9)
Net cash provided by financing activities	632	311,348
Net cash increase (decrease) for the period	(50,212)	286,958
Cash, cash equivalents and restricted cash at beginning of the period	302,425	15,467
Cash, cash equivalents and restricted cash at end of the period	$ 252,213	$ 302,425
Reconciliation of cash, cash equivalents and restricted cash to the balance sheet		
Cash and cash equivalents	$ 251,213	$ 302,182
Restricted cash	1,000	243
Total cash, cash equivalents and restricted cash	$ 252,213	$ 302,425
Supplemental disclosure of cash flow information:		
Right-of-use asset obtained in exchange for lease liability	$ 1,572	$ 1,238
Non-cash investing and financing activities:		
Conversion of convertible preferred stock in connection with initial public offering	—	157,274
Purchases of equipment included in accounts payable	—	209

See accompanying notes to financial statements.

1. Organization and Basis of Presentation

Organization

Tyra Biosciences, Inc. (the Company) was incorporated in the state of Delaware on August 2, 2018. The Company is a clinical-stage biotechnology company focused on developing next-generation precision medicines that target large opportunities in Fibroblast Growth Factor Receptor (FGFR) biology. The Company's in-house precision medicine platform, SNÅP, enables rapid and precise drug design through iterative molecular SNÅPshots that help predict genetic alterations most likely to cause acquired resistance to existing therapies. The Company's initial focus is on applying accelerated small molecule drug discovery engine to develop therapies in targeted oncology and genetically defined conditions.

Since its inception, the Company has devoted substantially all of its resources to research and development activities, business planning, establishing and maintaining its intellectual property portfolio, hiring personnel, raising capital, and providing general and administrative support for these operations. It has incurred losses and negative cash flows from operations since commencement of its operations. The Company had an accumulated deficit of $95.7 million and cash and cash equivalents of $251.2 million as of December 31, 2022. From its inception through December 31, 2022, the Company has financed its operations primarily through the sale of common stock and private placements of its convertible preferred stock.

As the Company continues its expansion, it may seek additional financing and/or strategic investments, however, there can be no assurance that any additional financing or strategic investments will be available to the Company on acceptable terms, if at all. If events or circumstances occur such that the Company does not obtain additional funding, it will most likely be required to reduce its plans and/or certain discretionary spending, which could have a material adverse effect on the Company's ability to achieve its intended business objectives. Management believes that it has sufficient working capital on hand to fund operations through at least the next twelve months from the date of issuance of these financial statements.

On September 17, 2021, the Company completed its initial public offering (the IPO) and issued 12,420,000 shares of common stock for net proceeds of approximately $181.2 million.

Basis of Presentation

The accompanying financial statements have been prepared in accordance with accounting principles generally accepted in the United States (GAAP). Any reference in these notes to applicable guidance is meant to refer to GAAP as found in the Accounting Standards Codification (ASC) and Accounting Standards Updates (ASU) promulgated by the Financial Accounting Standards Board (FASB).

2. Summary of Significant Accounting Policies

Use of Estimates

The preparation of financial statements in conformity with GAAP requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities and disclosure of contingent assets and liabilities at the date of the financial statements and the reported amounts of expenses during the reporting period. Accounting estimates and management judgments reflected in the financial statements include: normal recurring accruals, including the accrual of research and development expenses and stock-based compensation. Although these estimates are based on the Company's knowledge of current events and actions it may undertake in the future, actual results may materially differ from these estimates and assumptions.

Concentration of Credit Risk

Financial instruments which potentially subject the Company to significant concentration of credit risk consist of cash and cash equivalents. The Company maintains deposits in federally insured financial institutions in excess of federally insured limits. The Company has not experienced any losses in such accounts, and management believes that the Company is not exposed to significant credit risk due to the nature of the instruments held in the depository institutions.

Segment Reporting

The Company operates and manages its business as one operating segment. The Company's Chief Executive Officer, who is the chief operating decision maker, reviews financial information on an aggregate basis for allocating resources and evaluating financial performance. All long-lived assets are maintained in the United States.

Fair Value of Financial Instruments

The accounting guidance defines fair value, establishes a consistent framework for measuring fair value, and expands disclosure for each major asset and liability category measured at fair value on either a recurring or nonrecurring basis. Fair value is defined as an exit price representing the amount that would be received to sell an asset or paid to transfer a liability in an orderly transaction between market participants. As such, fair value is a market-based measurement that should be determined based on assumptions that market participants would use in pricing an asset or liability.

The carrying amounts of all cash and cash equivalents, prepaid and other current assets, restricted cash, accounts payable, and accrued and other current liabilities are considered to be representative of their respective fair values because of the short-term nature of those instruments.

Cash and Cash Equivalents

The Company considers all highly liquid investments with an original maturity of three months or less at the date of purchase to be cash equivalents. Cash equivalents primarily represent funds invested in readily available money market accounts. As of December 31, 2022, the Company had cash and cash equivalents balances deposited at major financial institutions.

Restricted Cash

Restricted cash is comprised of cash that is restricted as to withdrawal or use under the terms of certain contractual agreements. Restricted cash as of December 31, 2022 and 2021 was $1.0 million and $0.2 million, respectively, which consisted of collateral for letters of credit related to the Company's operating leases which are considered a non-current asset on the balance sheets.

Property and Equipment

Property and equipment is stated at cost and depreciated using the straight-line method over the estimated useful lives of the assets (generally three to seven years, or the remaining term of the lease).

Impairment of Long-Lived Assets

The Company accounts for the impairment of long-lived assets by reviewing these assets for impairment whenever events or changes in circumstances indicate that the carrying amount of an asset may not be recoverable. If circumstances require a long-lived asset or asset group to be tested for possible impairment, the Company first compares undiscounted cash flows expected to be generated by that asset or asset group to its carrying value. If the carrying value of the long-lived asset or asset group is not recoverable on an undiscounted-cash-flow basis, an

impairment is recognized to the extent that the carrying value exceeds its fair value. The Company did not recognize impairment losses for the years December 31, 2022 and 2021.

Accrued Research and Development Expense

Research and development expenses consist of external and internal costs associated with the Company's research and development activities, including its discovery and research efforts and the preclinical and clinical development of its product candidates. Research and development costs are expensed in the period incurred.

The Company has entered into various research and development contracts with clinical research organizations, clinical manufacturing organizations, clinical sites and other vendors and consultants. Payments for these activities are based on the terms of the individual agreements, which may differ from the pattern of costs incurred, and payments made in advance of or after performance are reflected in the accompanying balance sheets as prepaid expenses or accrued liabilities, respectively. The Company records accruals for estimated costs incurred for ongoing research and development activities. When evaluating the adequacy of the accrued liabilities, the Company analyzes progress of the services, including the phase or completion of events, invoices received and contracted costs. The Company holds discussions with applicable personnel and outside service providers as to the progress of clinical trials, or the services completed. Significant judgments and estimates may be made in determining the prepaid or accrued balances at the end of any reporting period. Actual results could differ from the Company's estimates. Nonrefundable advance payments for goods and services, including fees for process development, are deferred and recognized as expense in the period that the related goods are consumed, or services are performed.

Patent Costs

The Company expenses all costs as incurred in connection with patent applications (including direct application fees, and the legal and consulting expenses related to making such applications) and such costs are included in general and administrative expenses in the statements of operations and comprehensive loss.

Leases

The Company has operating leases for office and lab space. At the inception of a contractual arrangement, the Company determines whether the contract contains a lease by assessing whether there is an identified asset and whether the contract conveys the right to control the use of the identified asset in exchange for consideration over a period of time. If both criteria are met, the Company records the associated lease liability and corresponding right-of-use asset (ROU) upon commencement of the lease using the implicit rate or a discount rate based on a credit-adjusted secured borrowing rate commensurate with the term of the lease. The Company additionally evaluates leases at their inception to determine if they are to be accounted for as an operating lease or a finance lease.

Operating lease assets represent a right to use an underlying asset for the lease term and operating lease liabilities represent an obligation to make lease payments arising from the lease. Operating lease liabilities with a term greater than one year and their corresponding ROUs are recognized on the balance sheet at the commencement date of the lease based on the present value of lease payments over the expected lease term. The Company excludes short-term leases, if any, having initial terms of 12 months or less at lease commencement as an accounting policy election.

Certain adjustments to the ROU may be required for items such as payments made at or before the commencement date, initial direct costs paid or lease incentives received. As the Company's leases do not typically provide an implicit rate, the Company utilizes the appropriate incremental borrowing rate (IBR), determined as the rate of interest that the Company would have to pay to borrow on a collateralized basis over a similar term and in a similar economic environment. Lease cost is recognized on a straight-line basis over the lease term and variable lease payments are recognized as operating expenses in the period in which the obligation for those payments is incurred. Variable lease payments primarily include common area maintenance, utilities, real estate taxes, insurance, and other operating costs that are passed on from the lessor in proportion to the space leased by the Company. In measuring the ROU assets and lease liabilities, the Company has elected to combine lease and non-lease components.

Operating ROU assets are reflected in ROU assets in the accompanying balance sheets. Operating lease liabilities are reflected in leases liabilities, current and noncurrent in the accompanying balance sheets.

Stock-Based Compensation

Stock-based compensation expense represents the cost of the grant date fair value of employee, officer, director and non-employee equity awards, estimated in accordance with the applicable accounting guidance, and, for those awards subject only to service conditions, recognized on a straight-line basis over the vesting period. The vesting period generally approximates the expected service period of the awards. The Company recognizes stock-based compensation expense for awards with performance conditions when it is probable that the condition will be met, and the award will vest. If the achievement of performance conditions is no longer deemed probable, previously recognized compensation cost is reversed. For awards with performance and service conditions, the Company begins recording share-based compensation when achieving the performance criteria is probable and recognizes the costs using the accelerated attribution method. The Company recognizes forfeitures as they occur.

The fair value of stock options is estimated using a Black-Scholes valuation model on the date of grant. This method requires certain assumptions be used as inputs, such as the fair value of the underlying common stock, expected term of the option before exercise, expected volatility of the Company’s common stock, risk-free interest rate and expected dividend. Options granted have a maximum contractual term of ten years. The Company has limited historical stock option activity and therefore estimates the expected term of stock options granted using the simplified method, which represents the arithmetic average of the original contractual term of the stock option and its weighted-average vesting term. The expected volatility of stock options is estimated based on the average historical volatilities of common stock of comparable publicly traded companies and Company's own volatility. The comparable companies are chosen based on their size and stage in the life cycle. The Company will continue to apply this process until a sufficient amount of historical information regarding the volatility of its own stock price becomes available. The risk-free interest rates used are based on the U.S. Treasury yield in effect at the time of grant for zero-coupon U.S. treasury notes with maturities approximately equal to the expected term of the stock options. The Company has historically not declared or paid any dividends and does not currently expect to do so in the foreseeable future, and therefore has estimated the dividend yield to be zero.

Commitments and Contingencies

The Company recognizes a liability with regard to loss contingencies when it believes it is probable a liability has been incurred, and the amount can be reasonably estimated. If some amount within a range of loss appears at the time to be a better estimate than any other amount within the range, the Company accrues that amount. When no amount within the range is a better estimate than any other amount the Company accrues the minimum amount in the range.

Income Taxes

The Company accounts for income taxes under the asset and liability method, which requires the recognition of deferred tax assets and liabilities for the expected future tax consequences of events that have been included in the financial statements. Under this method, deferred tax assets and liabilities are determined on the basis of the differences between the financial statements and tax basis of assets and liabilities using enacted tax rates in effect for the year in which the differences are expected to reverse. The effect of a change in tax rates on deferred tax assets and liabilities is recognized in the statement of operations in the period that includes the enactment date.

The Company recognizes deferred tax assets to the extent that the Company believes these assets are more likely than not to be realized. In making such a determination, management considers all available positive and negative evidence, including future reversals of existing taxable temporary differences, projected future taxable income, tax-planning strategies, and results of recent operations. If management determines that the Company would be able to realize its deferred tax assets in the future in excess of their recorded amount, management would make an adjustment to the deferred tax asset valuation allowance, which would reduce the provision for income taxes.

As of December 31, 2022 and 2021, the Company maintained valuation allowances against its deferred tax assets as the Company concluded it had not met the "more likely than not" to be realized threshold. Changes in the valuation allowance when they are recognized in the provision for income taxes may result in a change in the estimated annual effective tax rate.

The Company records uncertain tax positions on the basis of a two-step process whereby (1) management determines whether it is more likely than not that the tax positions will be sustained on the basis of the technical merits of the position and (2) for those tax positions that meet the more-likely-than-not recognition threshold, management recognizes the largest amount of tax benefit that is more than 50 percent likely to be realized upon ultimate settlement with the related tax authority. The Company recognizes interest and penalties related to unrecognized tax benefits within income tax expense. Any accrued interest and penalties are included within the related tax liability. As of December 31, 2022, the Company had no accrued interest or penalties.

Comprehensive Loss

Comprehensive loss is defined as a change in equity during a period from transactions and other events and circumstances from non-owner sources. The Company's comprehensive loss was the same as its reported net loss for all periods presented.

Net Loss Per Share

Basic net loss per share is calculated by dividing the net loss by the weighted-average number of common shares outstanding for the period. Diluted net loss per share is computed by dividing the net loss by the weighted-average number of shares of common stock and common stock equivalents outstanding for the period. Common stock equivalents are only included when their effect is dilutive. The Company's potentially dilutive securities include unvested common stock, unvested common stock upon early exercise of stock options and outstanding stock options under the Company's equity incentive plan and have been excluded from the computation of diluted net loss per share as their inclusion would be antidilutive. For all periods presented, there is no difference in the number of shares used to calculate basic and diluted shares outstanding due to the Company's net loss position.

Related Parties

Transactions between related parties are considered to be related party transactions even though they may not be given accounting recognition. FASB ASC 850, Related Party Disclosures (FASB ASC 850) requires that transactions with related parties that would make a difference in decision making shall be disclosed so that users of the financial statements can evaluate their significance. Related party transactions typically occur within the context of the following relationships:

- Affiliates of the entity;
- Entities for which investments in their equity securities is typically accounted for under the equity method by the investing entity;
- Trusts for the benefit of employees;
- Principal owners of the entity and members of their immediate families;
- Management of the entity and members of their immediate families;
- Other parties that can significantly influence the management or operating policies of the transacting parties and can significantly influence the other to an extent that one or more of the transacting parties might be prevented from fully pursuing its own separate interests.

The Company previously entered into a consulting agreement with van den Boom & Associates, LLC (van den Boom & Associates), a professional services firm contracted to provide resources to assist with day-to-day accounting functions. Services provided under the agreement with van den Boom & Associates are billed at hourly rates. On April 16, 2021, Ms. van den Boom, the managing partner of van den Boom & Associates, entered into an employment agreement with the Company whereby she became its Chief Financial Officer. Van den Boom & Associates is considered a related party under FASB ASC 850 from the point in which Ms. van den Boom became a Company officer. On October 28, 2022, Ms. van den Boom informed the Company of her intent to resign as the Chief Financial Officer, effective December 31, 2022. From the date of the employment agreement with Ms. van den Boom to December 31, 2021, van den Boom & Associates rendered contracted services totaling approximately $0.5 million. For the year ended December 31, 2022, van den Boom & Associated rendered contracted services totaling approximately $0.8 million.

Recently Adopted Accounting Principles

There were no accounting principles adopted during the year ended December 31, 2022, which had a material impact on the financial statements.

Recently Issued Accounting Pronouncements

There were no recently issued accounting pronouncements that would materially impact the Company's financial statements and related disclosures for the years ended December 31, 2022 and 2021. Although there were several other new accounting pronouncements issued or proposed by the FASB, the Company does not believe any of those accounting pronouncements have had or will have a material impact on its financial position or operating results.

3. Fair Value Measurements

The accounting guidance defines fair value, establishes a consistent framework for measuring fair value and expands disclosure for each major asset and liability category measured at fair value on either a recurring or nonrecurring basis. Fair value is defined as an exit price, representing the amount that would be received to sell an asset or paid to transfer a liability in an orderly transaction between market participants. As such, fair value is a market-based measurement that should be determined based on assumptions that market participants would use in pricing an asset or liability. As a basis for considering such assumptions, the accounting guidance establishes a three-tier fair value hierarchy, which prioritizes the inputs used in measuring fair value as follows:

Level 1—Unadjusted quoted prices in active markets that are accessible at the measurement date for identical, unrestricted assets or liabilities.

Level 2—Quoted prices for similar assets and liabilities in active markets, quoted prices in markets that are not active, or inputs which are observable, either directly or indirectly, for substantially the full term of the asset or liability.

Level 3—Prices or valuation techniques that require inputs that are both significant to the fair value measurement and unobservable (i.e. supported by little or no market activity).

The carrying amounts of the Company's financial instruments, including cash and cash equivalents, prepaid and other current assets, restricted cash, accounts payable, and accrued and other current liabilities, approximate fair value due to their short maturities.

Assets measured at fair value on a recurring basis are as follows (in millions):

		Fair Value Measurements Using		
	As of December 31, 2022	Quoted Prices in Active Markets for Identical Assets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Cash equivalents:				
Money Market Funds	$ 240.7	$ 240.7	$ —	$ —

		Fair Value Measurements Using		
	As of December 31, 2021	Quoted Prices in Active Markets for Identical Assets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Cash equivalents:				
Money Market Funds	$ 291.7	$ 291.7	$ —	$ —

None of the Company's non-financial assets or liabilities are recorded at fair value on a non-recurring basis.

4. Property and Equipment

Property and equipment consisted of the following (in thousands):

	December 31,	
	2022	2021
Equipment	$ 1,119	$ 870
Computers and software	181	109
Leasehold improvements	156	141
Furniture and fixtures	82	76
	1,538	1,196
Less: accumulated depreciation	(461)	(169)
Total property and equipment, net	$ 1,077	$ 1,027

The Company recognized $296,000 and $140,000 in depreciation expense for the years ended December 31, 2022 and 2021, respectively.

5. Accrued and Other Current Liabilities

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

	December 31,	
	2022	2021
Accrued payroll and other employee benefits	$ 2,854	$ 1,278
Accrued research and development	1,028	1,257
Accrued legal and professional fees	94	61
Accrued other general and administrative fees	440	219
Total accrued and other current liabilities	$ 4,416	$ 2,815

6. Stockholders' Equity and Convertible Preferred Stock

Convertible Preferred Stock

In January 2020 and February 2021, the Company issued, at each date, 2,848,486 shares of Series A convertible preferred stock at a price of $8.25 per share resulting in net proceeds of $23.3 million and $23.5 million, respectively, excluding issuance costs of $0.2 million and $5,000, respectively.

In March 2021, the Company issued 3,874,793 shares of Series B convertible preferred stock, at a price of $27.4337 per share, resulting in net proceeds of $106.1 million excluding issuance costs of $0.2 million.

In September 2021, upon completion of the IPO, all of the Company's shares of convertible preferred stock converted into 26,228,089 shares of common stock.

Common Stock

Common stock reserved for future issuance consisted of the following:

	December 31,	
	2022	2021
Common stock options granted and outstanding	5,890,869	3,771,516
Shares available for future issuance under the 2021 Incentive Award Plan	4,339,373	4,384,274
Shares available for future issuance under the 2021 Employee Stock Purchase Plan	759,442	380,000
Total common stock reserved for future issuance	10,989,684	8,535,790

On October 3, 2022, the Company entered into the Sales Agreement with the Agent, under which the Company may, from time to time, sell shares of its common stock having an aggregate offering price of up to $150.0 million in "at the market" offerings through the Agent. Sales of the shares of common stock, if any, will be made at prevailing market prices at the time of sale, or as otherwise agreed with the Agent. The Agent will receive a commission from the Company of up to 3.0% of the gross proceeds of any shares of common stock sold under the Sales Agreement. During the year ended December 31, 2022, no shares of common stock were issued and sold pursuant to the Sales Agreement.

Restricted Stock

Since inception, the Company has issued 2,820,560 shares of restricted common stock at a price of $0.0001 per share to certain founders of the Company (Founders Stock). The Company maintains a repurchase right whereby the shares of Founders Stock are released from such repurchase right over a period of time of continued service by the recipient. Any shares subject to repurchase by the Company are not deemed to be outstanding, for accounting purposes, until those shares vest. Unvested outstanding Founders Stock as of December 31, 2022 and

2021 were 3,828 and 495,170 shares, respectively. The amount recorded as liabilities associated with shares issued with repurchase rights were immaterial as of December 31, 2022 and 2021.

For the years ended December 31, 2022 and 2021, 491,342 and 496,008 shares vested in each period and the Company recognized $0.3 million of stock-based compensation expense for each period related to the awards. As of December 31, 2022, the total unrecognized compensation expense related to unvested Founders Stock was immaterial.

7. Equity Incentive Plans and Stock-Based Compensation

Equity Incentive Plans

In September 2021, the Company's Board of Directors adopted, and its stockholders approved, the 2021 Incentive Award Plan (the 2021 Plan). Upon the adoption of the 2021 Plan, the Company restricted the grant of future equity awards under the 2020 Equity Incentive Plan (the 2020 Plan).

The 2021 Plan provides for the grants of stock options and other equity-based awards to employees, non-employee directors, and consultants of the Company. A total of 5,570,000 shares of the Company’s common stock were initially reserved for issuance pursuant to the 2021 Plan. In addition to the 4,537,850 reserved shares, the number of shares reserved under the 2021 Plan also included 1,032,150 shares of the Company’s common stock that remained available for issuance under the 2020 Plan as of immediately prior to the effectiveness of the 2021 Plan. The 2021 Plan share reserve will be increased by the number of shares under the 2020 Plan that are repurchased, forfeited, expired or cancelled after the effective date of the 2021 Plan. In addition, the number of shares of the Company’s common stock available for issuance under the 2021 Plan will automatically increase on the first day of each fiscal year, beginning with the Company’s 2022 fiscal year, in an amount equal to the lesser of (1) 5% of the outstanding shares of the Company’s common stock on the last day of the immediately preceding fiscal year, or (2) such smaller amount as determined by the Company’s Board of Directors. On January 1, 2022, the number of shares reserved for issuance under the 2021 Plan was increased to 7,696,809 shares. As of December 31, 2022, 4,339,373 shares were authorized for issuance under the 2021 Plan, inclusive of shares added from cancellations under the 2020 Plan.

A summary of the Company’s stock option activity for the year ended December 31, 2022 is as follows (in thousands, except share and per share data and years):

	Options	Weighted-Average Exercise Price per Share	Weighted-Average Remaining Contractual Term	Aggregate Intrinsic Value
Outstanding at December 31, 2021	3,771,516	$ 9.18	9.3	$ 28,901
Granted	2,685,077	$ 7.71		
Exercised	(52,357)	$ 4.90		
Cancelled	(513,367)	$ 14.84		
Outstanding at December 31, 2022	5,890,869	$ 7.91	8.8	$ 13,492
Exercisable at December 31, 2022	1,623,928	$ 6.80	8.3	$ 6,211
Vested and expected to vest as of December 31, 2022	5,890,869	$ 7.91	8.8	$ 13,492

Stock-Based Compensation Expense

The Company estimated the fair value of stock options using the Black-Scholes valuation model. The Company accounts for forfeitures of options when they occur. Previously recognized compensation expense for an award is reversed in the period that the award is forfeited. The fair value of stock options was estimated using the following assumptions (excluding option modifications):

	Year Ended December 31,	
	2022	2021
Stock Options:		
Stock price	$5.38 - 12.57	$0.99 - 24.15
Risk-free rate of interest	1.6 - 4.3%	0.8 - 1.4%
Expected term (years)	5.1 - 6.1	5.0 - 6.1
Expected stock price volatility	82.3 - 90.4%	88.2 - 99.9%
Dividend yield	—	—

Stock-based compensation expense recognized for all equity awards has been reported in the statements of operations and comprehensive loss as follows (in thousands):

	Year Ended December 31,	
	2022	2021
Research and development expense	$ 4,914	$ 1,341
General and administrative expense	5,674	1,546
Total	$ 10,588	$ 2,887

The weighted-average grant date fair value of options granted for the years ended December 31, 2022 and 2021 was $5.62 and $7.74 per share, respectively.

During the year ended December 31, 2022, 96,431 performance-based stock options vested upon the achievement of the performance condition. The Company recorded $1.2 million of compensation expense relating to the vested performance-based stock options for the year ended December 31, 2022.

For the year ended December 31, 2022, forfeitures resulted in the reversal of compensation expense totaling $1.2 million, of which $1.0 million related to compensation expense for performance-based options, previously recorded in 2022. An aggregate of 93,388 performance-based stock options were forfeited as the related performance conditions were not achieved.

Forfeitures resulting in the reversal of compensation expense were immaterial for the year ended December 31, 2021.

As of December 31, 2022, the unrecognized compensation cost related to options was $23.3 million, and is expected to be recognized as expense over a weighted-average period of approximately 2.5 years.

Option Modifications

During the year ended December 31, 2022, two executive officers' options were modified. The changes resulted in the recognition of additional stock-based compensation expense of $2.0 million recorded within general and administrative expenses, including $1.2 million related to accelerated vesting pursuant to the executive's original employment agreement and incremental stock-based compensation expense of $0.8 resulting from modified option terms.

Employee Stock Purchase Plan

In September 2021, the Company's Board of Directors approved and adopted the 2021 Employee Stock Purchase Plan (ESPP). The ESPP was subsequently approved by the stockholders on September 7, 2021. The ESPP became effective on the business day immediately prior to the effective date of the Company's first registration statement. A total of 380,000 shares of the Company's common stock were initially reserved for issuance pursuant to the ESPP. In addition, the number of shares of the Company's common stock available for issuance under the ESPP will automatically increase on the first day of each fiscal year, beginning with the Company's 2022 fiscal year, in an amount equal to the lesser of (1) 1% of the outstanding shares of the Company's common stock on the last day of the immediately preceding fiscal year, or (2) such smaller amount as determined by the Company's Board of Directors. On January 1, 2022, the number of shares reserved for issuance under the 2021 Employee Stock Purchase Plan was increased to 805,361 shares.

The ESPP permits eligible employees who elect to participate in an offering under the ESPP to have up to 15% of their eligible earnings withheld, subject to certain limitations, to purchase shares of common stock pursuant to the ESPP. The price of common stock purchased under the ESPP is equal to 85% of the lower of the fair market value of the common stock at the commencement date of each offering period or the relevant date of purchase. Each offering period is twenty-four months, with new offering periods commencing every six months on or about the dates of March 15 and September 15 of each year. During the years ended December 31, 2022 and 2021, the Company issued 45,919 and 0 shares, respectively, of common stock in connection with the ESPP. As of December 31, 2022, there were 759,442 shares available for future purchase under the ESPP.

The Company estimated the fair value of shares purchased under the ESPP, using the Black-Scholes valuation model. The fair value of shares purchased under the ESPP was estimated using the following assumptions:

	Year Ended December 31,	
	2022	2021
Stock Options:		
Stock price	$7.74 - 11.03	$16.00
Risk-free rate of interest	0.9 - 4.0%	0.0 - 0.3%
Expected term (years)	0.5 - 2.0	0.5 - 2.0
Expected stock price volatility	74.7 - 89.8%	69.7 - 92.4%
Dividend yield	—	—

During the years ended December 31, 2022 and 2021, the Company recognized compensation expense of $0.4 million and $0.1 million, respectively, related to the ESPP. As of December 31, 2022, the remaining unrecognized compensation expense related to the ESPP was $0.5 million, and is expected to be recognized as expense over a weighted-average period of approximately 1.1 years.

Liability for Early Exercise of Stock Options

Certain individuals were granted the ability to early exercise their stock options. The shares of common stock issued from the early exercise of unvested stock options are restricted and continue to vest in accordance with the original vesting schedule. The Company has the option to repurchase any unvested shares at the original purchase price upon any voluntary or involuntary termination. The shares purchased by the employees and non-employees pursuant to the early exercise of stock options are not deemed, for accounting purposes, to be outstanding until those shares vest. The cash received in exchange for exercised and unvested shares related to stock options granted is recorded as a liability for the early exercise of stock options on the accompanying balance sheets and will be transferred into common stock and additional paid-in capital as the shares vest. As of December 31, 2022 and 2021, 277,081 and 599,878 unvested shares issued under early exercise provisions were subject to repurchase by the Company, respectively. As of December 31, 2022 and 2021, the Company recorded $0.2 million and $0.4 million, respectively, associated with early exercised stock options in other long-term liabilities.

8. Net Loss Per Share

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

	Year Ended December 31,	
	2022	2021
Numerator:		
Net loss	$ (55,325)	$ (26,294)
Denominator:		
Weighted-average common shares outstanding	42,627,825	15,206,879
Less: weighted-average unvested restricted common stock subject to repurchase	(269,174)	(732,418)
Less: weighted-average unvested common stock issued upon early exercise of common stock options	(474,746)	(693,915)
Weighted-average shares used to compute net loss per common share, basic and diluted	41,883,904	13,780,546
Net loss per share, basic and diluted	$ (1.32)	$ (1.91)

The following table sets forth the outstanding potentially dilutive securities that have been excluded from the calculation of diluted net loss per share because their inclusion would be anti-dilutive.

	As of December 31,	
	2022	2021
Unvested restricted common stock subject to repurchase	3,828	495,170
Unvested common stock upon early exercise of stock options	277,081	599,878
Options to purchase common stock	5,890,869	3,771,516
	6,171,778	4,866,564

9. Income Taxes

The following is a reconciliation between the provision for income taxes and income taxes computed using the U.S. federal statutory corporate tax rate for the years ended December 31, 2022 and 2021 is as follows (in thousands):

	Year Ended December 31,	
	2022	2021
Expected tax benefit at statutory rate	$ (11,618)	$ (5,392)
State income tax, net of federal benefit	(58)	(1,661)
Officers compensation	598	28
Permanent items and other	707	86
Research credits	(2,093)	(680)
Change in valuation allowance	12,466	7,620
Provision for income taxes	$ 2	$ 1

The tax effects of temporary differences that give rise to significant portions of the deferred tax assets and deferred tax liabilities as of December 31, 2022 and 2021 are as follows (in thousands):

	As of December 31,	
	2022	2021
Deferred tax assets:		
Net operating loss carryforwards	$ 11,596	$ 9,297
Capitalized research and development	7,097	—
Tax credits	2,958	874
Stock compensation	1,016	239
Other, net	1,090	470
Total deferred tax assets	23,757	10,880
Valuation allowance	(23,085)	(10,618)
Deferred tax assets, net of valuation allowance	672	262
Deferred tax liabilities:		
Depreciation	(151)	(37)
Right of use assets	(521)	(225)
Total deferred tax liabilities	(672)	(262)
Net deferred tax assets / (liabilities)	$ —	$ —

The Company has established a valuation allowance against its net deferred tax assets due to the uncertainty surrounding the realization of such assets. The Company periodically evaluates the recoverability of the deferred tax assets. At such time as it is determined that it is more likely than not that deferred assets are realizable, the valuation allowance will be reduced. The Company has recorded a full valuation allowance of $23.1 million as of December 31, 2022 as management cannot conclude that it is more likely than not that certain deferred tax assets will be realized primarily due to the history of losses from inception. The Company increased its valuation allowance by approximately $12.5 million during the year ended December 31, 2022.

At December 31, 2022, the Company had federal and state tax loss carry forwards of approximately $46.0 million and $35.9 million, respectively. As a result of the Tax Cuts and Jobs Act of 2017, for U.S. income tax purposes, net operating losses generated after December 31, 2017 can be carried forward indefinitely, but are limited to 80% utilization against future taxable income each year. Of the amount of federal and state net operating loss carryforwards, $46.0 million and $1.1 million, respectively, can be carried forward indefinitely. Unless previously utilized, certain state net operating losses will begin to expire in 2038.

In accordance with the 2017 Tax Cuts and Jobs Act, research and experimental (R&E) expenses under Internal Revenue Code (IRC) Section 174 are required to be capitalized beginning in 2022. R&E expenses are

required to be amortized over a period of five years for domestic expenses and 15 years for foreign expenses. The Company has capitalized R&E expenses in its current tax provision pursuant to the IRC Section 174.

At December 31, 2022, the Company has federal and California research and development tax credits of $2.7 million and $1.3 million, respectively. The federal research and development tax credits begin to expire in 2038 unless previously utilized. The California research and development tax credits carry forward indefinitely.

Pursuant to the IRC Sections 382 and 383, annual use of the Company's NOL and research and development credit carryforwards may be limited in the event a cumulative change in ownership of more than 50% occurs within a three-year period. The Company has not completed an ownership change analysis pursuant to IRC Section 382. If ownership changes have occurred or occurs in the future, the amount of remaining tax attribute carryforwards available to offset taxable income and income tax expense in future years may be restricted or eliminated. If eliminated, the related asset would be removed from deferred tax assets with a corresponding reduction in the valuation allowance.

Uncertain tax positions are evaluated based upon the facts and circumstances that exist at each reporting period. Subsequent changes in judgement based upon new information may lead to changes in recognition, derecognition, and measurement. Adjustment may result, for example, upon resolution of an issue with the taxing authorities or expiration of a statute of limitations barring an assessment for an issue.

The Company recognizes a tax benefit from an uncertain tax position when it is more likely than not that the position will be sustained upon examination by tax authorities.

The following table summarizes the changes to the Company's gross unrecognized tax benefits for the years ended December 31, 2022 and 2021, respectively (in thousands):

	Year Ended December 31,	
	2022	2021
Beginning balance at January 1	$ 1,142	$ 91
Additions related to current year positions	366	312
Additions related to prior year positions	66	739
Ending balance at December 31	$ 1,574	$ 1,142

Due to the existence of the valuation allowance, future recognition of previously unrecognized tax benefits will not impact the Company's effective tax rate. The Company is subject to taxation in the United States and various state jurisdictions. All of the Company's tax years from inception are subject to examination by federal and state tax authorities. The Company's practice is to recognize interest and penalties related to income tax matters in income tax expense.

The Company had no accrued interest or penalties related to income tax matters in the Company's balance sheet as of December 31, 2022 and has not recognized interest or penalties in the Company's statements of operations and comprehensive loss for the years ended December 31, 2022 and 2021. Further, the Company is not currently under examination by any federal, state or local tax authority.

The CARES Act provides sweeping tax changes in response to the COVID-19 pandemic. Some of the more significant provisions are removal of certain limitations on utilization of net operating losses, increasing the loss carryback period for certain losses to five years, and increasing the ability to deduct interest expense, as well as amending certain provisions of the previously enacted Tax Cuts and Jobs Act. As of December 31, 2022, the Company has not recorded any material adjustments to its income tax provision related to the provisions within the CARES Act. The Company will continue to analyze the impact that the CARES Act will have, if any, on its financial position, results of operations or cash flows.

10. Leases

The Company has operating leases for its office and laboratory space, including its corporate headquarters.

In August 2020, the Company entered into a lease agreement for approximately 4,734 square feet of office and lab space at 2656 State Street in Carlsbad, California, for the Company's headquarters (the Original Lease). The Original Lease commenced in May 2021, and had an original term of 60 months, with an option to extend for two additional 36 month periods. The lease agreement required the Company to provide a letter of credit for $0.2 million that is collateralized with cash that is recorded as restricted cash in the accompanying balance sheet. Additionally, in connection with the Original Lease, the Company paid a security deposit of approximately $21,000.

In March 2022, the Company entered into an agreement (the Expansion Lease) for an additional office and laboratory space. The Expansion Lease is expected to commence in the second half of 2023 and projected lease payments over the life of the lease are expected to be $5.5 million with a lease expiration of 120 months after the commencement of the Expansion Lease. The Company has an option to renew the Expansion Lease and its existing operating lease, which has the same lessor and has been amended to have the same lease term as the Expansion Lease for two additional thirty-six month periods.

In March 2022, the Original Lease was amended to extend the lease term to 120 months from the commencement of the Expansion Lease.

As the Company was not reasonably certain to exercise either the amended the Original Lease or the Expansion lease options at lease commencement, neither option was recognized as part of the associated operating lease ROU asset or liability.

Cash paid for amounts included in the measurement of lease liabilities was $0.3 million and $0.2 million for the years ended December 31, 2022 and 2021, respectively.

The components of lease expense include operating, finance, short-term, and variable lease costs. Amortization is recorded in research and development expenses and interest expense is recorded in other expenses in the statements of operations and comprehensive loss. Components of lease cost for the years ended December 31, 2022 and 2021, respectively, follows (in thousands):

	Year Ended December 31,	
	2022	2021
Operating lease cost	$ 322	$ 331
Finance lease cost		
Amortization of ROU assets	—	5
Short-term lease cost	81	73
Variable lease cost	56	16
Total Lease Cost	$ 459	$ 420

Maturities of lease liabilities, weighted-average remaining term and weighted-average discount rate were as follows (in thousands):

	As of December 31,
Year ending December 31,	
2023	$ 300
2024	309
2025	318
2026	328
Thereafter	2,381
Total minimum lease payments [1]	3,636
Less: amount representing interest	(1,014)
Present value of lease liabilities	2,622
Less: current portion of lease liabilities	(140)
Lease liabilities, noncurrent	$ 2,482

(1) Excludes $5.5 million of legally binding minimum lease payments for leases not yet commenced

	December 31,	
	2022	2021
Weighted-average remaining lease term (years) - operating leases	10.5	4.6
Weighted-average incremental borrowing rate - operating leases	6.50%	7.50%

11. Commitments and Contingencies

Other Funding Commitments

As of December 31, 2022, the Company had ongoing clinical and pre-clinical studies for its various pipeline programs. The Company enters into contracts in the normal course of business with contract research organizations in preparation for clinical trials, professional consultants for expert advice and other vendors for clinical supply manufacturing or other services. These contracts are generally cancellable, with notice, at the Company's option and do not have significant cancellation penalties.

Guarantees

The Company enters into certain agreements with other parties in the ordinary course of business that contain indemnification provisions. These typically include agreements with directors and officers, business partners, contractors, landlords, contract research organizations and clinical sites. Under these provisions, the Company generally indemnifies and holds harmless the indemnified party for losses suffered or incurred by the indemnified party under the terms of the contract, including as a result of the Company’s activities. These indemnification provisions generally survive termination of the underlying agreement. The maximum potential amount of future payments the Company could be required to make under these indemnification provisions is unlimited. However, to date the Company has not incurred material costs to defend lawsuits or settle claims related to these indemnification provisions. As a result, the estimated fair value of these obligations is minimal.

Litigation

The Company, from time to time, may be party to litigation arising in the ordinary course of business. The Company was not subject to any material legal proceedings as of December 31, 2022, and no material legal proceedings are currently pending or threatened. If the potential loss from any claim, asserted or unasserted, or legal proceeding is considered probable and the amount is reasonably estimable, the Company will accrue a liability for the estimated loss.

12. Employee Benefits

The Company offers a 401(k) plan (401(k) Plan) for all employees who have met certain eligibility requirements. Under the 401(k) Plan, employees may elect to contribute a portion of their eligible compensation, subject to certain limitations. The Company did not make any matching employer contributions to the 401(k) Plan for the years ended December 31, 2022 and 2021.

Item 9. Changes in and Disagreements With Accountants on Accounting and Financial Disclosure.

None.

Item 9A. Controls and Procedures.

Evaluation of Disclosure Controls and Procedures

Our management, with the participation of our chief executive officer and our chief financial officer (our principal executive officer and principal financial and accounting officer, respectively), evaluated the effectiveness of our disclosure controls and procedures as of December 31, 2022. The term "disclosure controls and procedures," as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act of 1934, as amended (the Exchange Act), means controls and other procedures of a company that are designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act is recorded, processed, summarized and reported within the time periods specified in the Securities and Exchange Commission (the SEC)'s rules and forms. Disclosure controls and procedures include, without limitation, controls and procedures designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act is accumulated and communicated to the company's management, including its principal executive and principal financial officers, as appropriate to allow timely decisions regarding required disclosure.

Our management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving their objectives and management necessarily applies its judgment in evaluating the cost-benefit relationship of possible controls and procedures. Based on the evaluation of our disclosure controls and procedures as of December 31, 2022, our chief executive officer and our chief financial officer concluded that, as of such date, our disclosure controls and procedures were effective at the reasonable assurance level.

Management’s Annual Report on Internal Control Over Financial Reporting

Our management is responsible for establishing and maintaining adequate internal control over financial reporting, as defined in Exchange Act Rules 13a-15(f). Management assessed our internal control over financial reporting as of December 31, 2022, and based its assessment on criteria established in "Internal Control - Integrated Framework (2013)" issued by the Committee of Sponsoring Organizations of the Treadway Commission (COSO). Based on that assessment, our management concluded that our internal control over financial reporting was effective as of December 31, 2022.

Attestation Report of the Registered Public Accounting Firm

This Annual Report does not include an attestation report of our registered public accounting firm due to an exemption provided by the JOBS Act for “emerging growth companies.”

Changes in Internal Control Over Financial Reporting

There were no changes in our internal control over financial reporting (as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act) during the quarter ended December 31, 2022 that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

Item 9B. Other Information.

None.

Item 9C. Disclosure Regarding Foreign Jurisdictions that Prevent Inspections.

Not applicable.

PART III

Item 10. Directors, Executive Officers and Corporate Governance.

Information required by this item will be contained in our definitive proxy statement to be filed with the SEC in connection with our 2023 Annual Meeting of Stockholders (the Definitive Proxy Statement), which is expected to be filed not later than 120 days after the end of our fiscal year ended December 31, 2022, under the headings "Election of Directors," "Corporate Governance," "Executive Officers," and "Section 16(a) Beneficial Ownership Reporting Compliance," and is incorporated herein by reference.

Code of Business Conduct and Ethics

We have adopted a Code of Business Conduct and Ethics that applies to our officers, directors and employees, which is available on our website at www.tyra.bio. The Code of Business Conduct and Ethics contains general guidelines for conducting the business of our company consistent with the highest standards of business ethics and is intended to qualify as a "code of ethics" within the meaning of Section 406 of the Sarbanes-Oxley Act of 2002 and Item 406 of Regulation S-K. In addition, we intend to promptly disclose (1) the nature of any amendment to our Code of Business Conduct and Ethics that applies to our principal executive officer, principal financial officer, principal accounting officer or controller or persons performing similar functions and (2) the nature of any waiver, including an implicit waiver, from a provision of our code of ethics that is granted to one of these specified officers, the name of such person who is granted the waiver and the date of the waiver on our website in the future.

Item 11. Executive Compensation.

Information required by this item will be contained in our Definitive Proxy Statement under the heading "Executive Compensation and Other Information," and is incorporated herein by reference.

Item 12. Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters.

Information required by this item will be contained in our Definitive Proxy Statement under the heading "Security Ownership of Certain Beneficial Owners and Management," and is incorporated herein by reference.

Information required by Item 201(d) of Regulation S-K will be contained in our Definitive Proxy Statement under the heading "Executive Compensation" and is incorporated herein by reference.

Item 13. Certain Relationships and Related Transactions, and Director Independence.

Information required by this item will be contained in our Definitive Proxy Statement under the headings "Certain Relationships and Related Person Transactions," "Board Independence" and "Committees of the Board of Directors" and is incorporated herein by reference.

Item 14. Principal Accounting Fees and Services.

Information required by this item will be contained in our Definitive Proxy Statement under the heading "Independent Registered Public Accountants' Fees," and is incorporated herein by reference.

PART IV

Item 15. Exhibits and Financial Statement Schedules.

1. Financial Statements.

The financial statements of Tyra Biosciences, Inc., together with the report thereon of Ernst & Young LLP, an independent registered public accounting firm (PCAOB ID No. 42), are included in this Annual Report contained in Part II, Item 8. Financial Statements and Supplementary Data.

2. Finance Statement Schedules.

All schedules are omitted because they are not applicable or the required information is shown in the financial statements or notes thereto.

3. Exhibits.

A list of exhibits is set forth on the Exhibit Index immediately preceding the signature page of this Annual Report and is incorporated herein by reference.

Item 16. Form 10-K Summary.

None.

EXHIBIT INDEX

Exhibit Number	Exhibit Description	Incorporated by Reference			Filed Herewith
		Form	Date	Number	
3.1	Amended and Restated Certificate of Incorporation				X
3.2	Amended and Restated Bylaws	8-K	9/17/21	3.2	
4.1	Specimen stock certificate evidencing the shares of common stock	S-1	8/20/21	4.1	
4.2	Amended and Restated Investors' Rights Agreement, dated March 5, 2021, by and among the Registrant and certain of its stockholders	S-1/A	9/9/21	4.2	
4.3	Description of Registered Securities	10-K	3/3/22	4.3	
10.1#	Tyra Biosciences, Inc. 2020 Equity Incentive Plan and form of stock option agreement thereunder	S-1	8/20/21	10.1	
10.2#	Tyra Biosciences, Inc. 2021 Incentive Award Plan and form of stock option grant notice and stock option agreement thereunder	S-1/A	9/9/21	10.2	
10.3#	Tyra Biosciences, Inc. 2021 Employee Stock Purchase Plan	S-1/A	9/9/21	10.3	
10.4#	Non-Employee Director Compensation Program	S-1/A	9/9/21	10.4	
10.5#	Tyra Biosciences, Inc. Annual Bonus Plan				X
10.6#	Second Amended and Restated Employment Letter Agreement, dated August 18, 2021, by and between Todd Harris and the Registrant	S-1	8/20/21	10.12	
10.7#	Second Amended and Restated Employment Letter Agreement, dated August 18, 2021, by and between Daniel Bensen and the Registrant	S-1	8/20/21	10.13	
10.8#	Amended and Restated Employment Letter Agreement, dated August 18, 2021, by and between Esther van den Boom and the Registrant	S-1	8/20/21	10.14	
10.9#	Amended and Restated Employment Letter Agreement, dated August 18, 2021, by and between Ronald Swanson and the Registrant	S-1	8/20/21	10.15	
10.10#	Amended and Restated Employment Letter Agreement, dated August 18, 2021, by and between Hiroomi Tada and the Registrant	S-1	8/20/21	10.16	
10.11#	Amended and Restated Employment Agreement, dated August 18, 2021, by and between Robert Hudkins and the Registrant	S-1	8/20/21	10.17	
10.12#	Amended and Restated Employment Letter Agreement, dated August 18, 2021, by and between Piyush Patel and the Registrant	S-1	8/20/21	10.18	
10.13#	Employment Letter Agreement, dated May 16, 2022, by and between Ali Fawaz and the Registrant	10-Q	8/4/2022	10.1	
10.14#	Employment Letter Agreement, dated December 31, 2022, by and between Alan Fuhrman and the Registrant				X
10.15#	Form of Indemnification Agreement for Directors and Officers	S-1	8/20/21	10.20	
10.16	Consulting Agreement, dated January 1, 2023, by and between Esther van den Boom and the Registrant				X
10.17	Office Lease, between the Registrant and Fabric 2656 State, LLC, a California limited liability company, dated August 5, 2020	S-1	8/20/21	10.19	

10.18	First Amendment to Lease, between the Registrant and Fabric 2656 State, LLC, a California limited liability company, dated March 2, 2022	10-K	3/3/22	10.14	
10.19	Second Amendment to Lease, between the Registrant and Fabric 2656 State, LLC, a California limited liability company, dated December 20, 2022				X
10.20	Office Lease, between the Registrant and Fabric 2676 State Street, LLC, a California limited liability company, dated March 2, 2022	10-K	3/3/22	10.15	
10.21	First Amendment to Lease, between the Registrant and Fabric 2676 State, LLC, a California limited liability company, dated May 16, 2022				X
10.22	Second Amendment to Lease, between the Registrant and Fabric 2676 State, LLC, a California limited liability company, dated January 6, 2023				X
10.23	ATM Sales Agreement, dated October 3, 2022, by and between Virtu Americas LLC and the Registrant	8-K	10/3/22	1.1	
23.1	Consent of independent registered public accounting firm				X
31.1	Certification of Chief Executive Officer, as required by Rule 13a-14(a) or Rule 15d-14(a), as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002				X
31.2	Certification of Chief Financial Officer, as required by Rule 13a-14(a) or Rule 15d-14(a), as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002				X
32.1*	Certification of Chief Executive Officer pursuant to Section 906 of the Sarbanes-Oxley Act of 2002				X
32.2*	Certification of Chief Financial Officer pursuant to Section 906 of the Sarbanes-Oxley Act of 2002				X
101.INS	Inline XBRL Instance Document - the Instance Document does not appear in the interactive data file because its XBRL tags are embedded within the Inline XBRL document				X
101.SCH	Inline XBRL Taxonomy Extension Schema Document				X
101.CAL	Inline XBRL Taxonomy Calculation Linkbase Document				X
101.DEF	Inline XBRL Taxonomy Extension Definition Linkbase Document				X
101.LAB	Inline XBRL Taxonomy Extension Label Linkbase Document				X
101.PRE	Inline XBRL Taxonomy Extension Presentation Linkbase Document				X
104	Cover Page Interactive Data File (embedded within the Inline XBRL Document)				X

# Indicates management contract or compensatory plan.
* This certification is deemed not filed for purpose of Section 18 of the Exchange Act or otherwise subject to the liability of that section, nor shall it be deemed incorporated by reference into any filing under the Securities Act or the Exchange Act.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized.

TYRA BIOSCIENCES, INC.

/s/ Todd Harris, Ph.D.
Todd Harris, Ph.D.
President, Chief Executive Officer, and Director

Date: March 22, 2023

Pursuant to the requirements of the Securities Exchange Act of 1934, this report has been signed below by the following persons on behalf of the registrant and in the capacities and on the dates indicated.

Name	Title	Date
/s/ Todd Harris, Ph.D. **Todd Harris, Ph.D.**	President, Chief Executive Officer and Director (principal executive officer)	March 22, 2023
/s/ Alan Fuhrman **Alan Fuhrman**	Chief Financial Officer (principal financial and accounting officer)	March 22, 2023
/s/ Isan Chen, M.D. **Isan Chen, M.D.**	Director	March 22, 2023
/s/ Gilla Kaplan, Ph.D. **Gilla Kaplan, Ph.D.**	Director	March 22, 2023
/s/ Nina Kjellson **Nina Kjellson**	Director	March 22, 2023
/s/ Melissa McCracken, Ph.D. **Melissa McCracken, Ph.D.**	Director	March 22, 2023
/s/ Robert More **Robert More**	Director	March 22, 2023
/s/ Jake Simson, Ph.D. **Jake Simson, Ph.D.**	Director	March 22, 2023
/s/ Siddarth Subramony, Ph.D. **Siddarth Subramony, Ph.D.**	Director	March 22, 2023
/s/ Rehan Verjee **Rehan Verjee**	Director	March 22, 2023