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 001-39122

89bio, Inc.

(Exact name of Registrant as specified in its Charter)

Delaware	**36-4946844**
(State or other jurisdiction of incorporation or organization)	**(I.R.S. Employer Identification No.)**
142 Sansome Street, Second Floor San Francisco, California 94104	**94104**
(Address of principal executive offices)	**(Zip Code)**

Registrant's telephone number, including area code: (415) 432-9270

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, par value $0.001 per share	ETNB	Nasdaq Global Market

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

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

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

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

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

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

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

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

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

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

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). ☐

The aggregate market value of the voting and non-voting common equity held by non-affiliates of the Registrant, based on the closing price of the shares of common stock on The Nasdaq Global Market on June 30, 2022, the last business day of the Registrant's most recently completed second fiscal quarter, was approximately $30.4 million. Shares of common stock held by each officer and director and by each person who is known to own 10% or more of the outstanding common stock have been excluded in that such persons may be deemed to be affiliates of the Registrant. This determination of affiliate status is not necessarily a conclusive determination for other purposes.

The number of shares of Registrant's common stock outstanding as of March 3, 2023 was 52,230,621.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the Registrant's definitive proxy statement relating to its 2023 Annual Meeting of Stockholders, to be held on or about May 31, 2023, are incorporated by reference into Part III of this Annual Report on Form 10-K where indicated. Such proxy statement will be filed with the U.S. Securities and Exchange Commission within 120 days after the end of the fiscal year to which this report relates.

Auditor Firm Id: 185 Auditor Name: KPMG LLP Auditor Location: San Francisco, California, USA

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FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K contains "forward-looking statements" within the meaning of the federal securities laws, which statements involve substantial risks and uncertainties. All statements, other than statements of historical facts included in this Annual Report on Form 10-K, including statements concerning our plans, objectives, goals, strategies, future events, future revenues or performance, financing needs, plans or intentions relating to acquisitions, business trends and other information referred to in "Business," "Risk Factors" and "Management's Discussion and Analysis of Financial Condition and Results of Operations" are forward-looking statements. Forward-looking statements generally relate to future events or our future financial or operating performance. In some cases, you can identify forward-looking statements by terms such as "may," "might," "will," "objective," "intend," "should," "could," "can," "would," "expect," "believe," "design," "estimate," "predict," "potential," "plan," "anticipate," "target," "forecast," or the negative of these terms, and similar expressions intended to identify forward-looking statements. Forward-looking statements are not historical facts and reflect our current views with respect to future events and are based on assumptions and subject to risks and uncertainties. Given these uncertainties, you should not place undue reliance on these forward-looking statements.

There are a number of risks, uncertainties and other important factors that could cause our actual results to differ materially from the forward-looking statements contained in this Annual Report on Form 10-K. Such risks, uncertainties and other important factors include, among others, the risks, uncertainties and factors set forth in "Risk Factors," and the following risks, uncertainties and factors:

- our plans to develop and commercialize pegozafermin (previously BIO89-100) or any future product candidates;
- our ongoing and planned clinical trials;
- the timing of and our ability to obtain regulatory approvals for pegozafermin or any future product candidates;
- our estimates regarding expenses, future revenue, capital requirements and needs for additional financing;
- our ability to obtain additional capital;
- the effect of the ongoing COVID-19 pandemic on our business;
- our ability to identify additional products or product candidates with significant commercial potential that are consistent with our commercial objectives;
- the rate and degree of market acceptance and clinical utility of pegozafermin or any future product candidates, if approved;
- our commercialization, marketing and manufacturing capabilities and strategy;
- substantial competition in our industry and with respect to the product candidates that we are developing;
- our intellectual property position;
- loss of key members of management;
- failure to successfully execute our growth strategy, including any delays in our planned future growth; and
- our failure to maintain effective internal controls.

There may be other factors that may cause our actual results to differ materially from the forward-looking statements, including factors disclosed in "Risk Factors" and "Management's Discussion and Analysis of Financial Condition and Results of Operations." You should evaluate all forward-looking statements made in this Annual Report on Form 10-K in the context of these risks and uncertainties.

We caution you that the risks, uncertainties and other factors referred to above may not contain all of the risks, uncertainties and other factors that are important to you. In addition, we cannot assure you that we will realize the results, benefits or developments that we expect or anticipate or, even if substantially realized, that they will result in the consequences or affect us or our business in the way expected. All forward-looking statements in this Annual Report on Form 10-K apply only as of the date made and are expressly qualified in their entirety by the cautionary statements included in this Annual Report on Form 10-K. We undertake no obligation to publicly update or revise any forward-looking statements to reflect subsequent events or circumstances.

PART I

In this Annual Report on Form 10-K, unless context otherwise requires or where otherwise indicated, the terms "89bio" "we," "us," "our," "our company," "the company," and "our business" refer to 89bio, Inc. and its consolidated subsidiaries.

Item 1. Business.

Overview

We are a clinical-stage biopharmaceutical company focused on the development and commercialization of innovative therapies for the treatment of liver and cardio-metabolic diseases. Our lead product candidate, pegozafermin (previously BIO89-100), a specifically engineered glycoPEGylated analog of fibroblast growth factor 21 ("FGF21"), is currently being developed for the treatment of nonalcoholic steatohepatitis ("NASH") and for the treatment of severe hypertriglyceridemia ("SHTG"). NASH is a severe form of nonalcoholic fatty liver disease ("NAFLD"), characterized by inflammation and fibrosis in the liver that can progress to cirrhosis, liver failure, hepatocellular carcinoma ("HCC") and death. There are currently no approved products for the treatment of NASH. In 2020 and 2022, we presented positive topline results from cohorts 1 through 6 and cohort 7, respectively, in our Phase 1b/2a trial of pegozafermin in NASH patients, which has informed the advancement of our clinical strategy in NASH. We initiated a Phase 2b trial (ENLIVEN) evaluating pegozafermin in fibrosis stage 2 or 3 NASH patients in June 2021. In the ENLIVEN trial, patients receive weekly doses or an every two-week dose of pegozafermin or placebo for 24 weeks followed by a blinded extension phase of an additional 24 weeks for a total treatment period of 48 weeks. ENLIVEN completed enrollment in August 2022 and we are expecting to report topline data from this trial in March 2023. In 2021, we completed a pharmacokinetic study of pegozafermin in NASH patients with compensated cirrhosis (fibrosis stage F4) demonstrating that a 30 mg dose of pegozafermin has similar single-dose pharmacokinetics and pharmacodynamics in F4 as it does in non-cirrhotic NASH. We are currently evaluating the potential opportunity for pegozafermin in these fibrosis stage F4 patients. We are also developing pegozafermin for the treatment of SHTG. In June 2022, we announced positive topline results from the ENTRIGUE Phase 2 trial of pegozafermin in SHTG patients. SHTG is a condition identified by severely elevated levels of triglycerides (≥500 mg/dL), which is associated with an increased risk of NASH, cardiovascular events and acute pancreatitis. The trial met its primary endpoint demonstrating statistically significant and clinically meaningful reductions in triglycerides from baseline and key secondary endpoints. We have received feedback from the FDA supporting the advancement of pegozafermin into Phase 3 and are planning to initiate the first of two recommended Phase 3 trials in the second quarter of 2023. In parallel, we have developed plans to optimize our clinical development program across both indications that would leverage the safety database from our SHTG Phase 3 program to support our NASH program. We expect to finalize these plans after we have reviewed results from the ENLIVEN trial.

FGF21 is a metabolic hormone that regulates energy expenditure and glucose and lipid metabolism. FGF21 analogs represent a promising class of drugs to treat NASH, because they not only address the liver manifestations, but also have an effect on the multiple co-morbidities that worsen NASH. FGF21 is a clinically validated mechanism that has been shown in humans to reduce steatosis, improve the histological features of NASH and address cardio-metabolic dysregulation. It is thought to exert effects on liver fibrosis by improving metabolic regulation, which reduces ongoing liver injury thus giving the liver time to heal. FGF21 also generates an on-target effect to increase adiponectin, a hormone released from adipose tissue that, among other functions, can suppress development and progression of hepatic fibrosis. However, FGF21 in its native form suffers from a short half-life and a tendency to aggregate in solution, both of which impact its suitability as a viable drug. To address these challenges, we have specifically engineered pegozafermin to extend the half-life of the molecule while maintaining potency and thereby the clinical benefits of FGF21.

Pegozafermin may be a differentiated FGF21 therapy based on its robust and durable biological effects, a favorable tolerability profile and its potential for every two-week dosing. Given its ability to address the key liver pathologies in NASH, as well as the underlying metabolic dysregulation in NASH patients, pegozafermin has the potential to become a backbone of treatment in NASH. Pegozafermin is the only FGF21 analog being developed for the treatment of SHTG and its broad metabolic effects could potentially differentiate it from competitors in this market. Pegozafermin has a long half-life which allows convenient weekly or every two-week dosing and is currently the only FGF21 analog being tested for every two-week dosing. The convenient dosing regimen may support adoption and compliance amongst patients living with these chronic and generally asymptomatic diseases. Pegozafermin is self-administered by patients subcutaneously in a liquid formulation. We have developed a new pre-filled syringe using our approved liquid formulation and plan to utilize this presentation in our planned SHTG Phase 3 trial in the second quarter of 2023.

Strategy

Our goal is to become a leading biopharmaceutical company focused on the development and commercialization of innovative therapies for the treatment of liver and cardio-metabolic diseases. The key components of our strategy are to:

- **Rapidly advance pegozafermin through clinical development for the treatment of NASH.** We believe pegozafermin may be a differentiated FGF21 therapy based on its robust and durable biological effects, a favorable tolerability profile and its potential for every two-week dosing. We have reported positive topline results from our Phase 1b/2a trial in NASH patients and have an ongoing Phase 2b trial (ENLIVEN) in NASH patients with F2 and F3 fibrosis that is expected to report topline data in March 2023. We are also evaluating the potential opportunity for pegozafermin in NASH patients with compensated cirrhosis.
- **Progress pegozafermin for the treatment of SHTG.** Pegozafermin's mechanism of action and profile relative to currently available therapies, as well as new therapies in development, support its potential to become a differentiated treatment for SHTG patients with metabolic co-morbidities. We reported positive topline results from our Phase 2 ENTRIGUE trial. Based on these positive results and defined regulatory path to approval based on FDA feedback, we plan to initiate the first Phase 3 trial in this indication in the second quarter of 2023.
- **Scale-up and optimize the manufacturing of pegozafermin.** We currently use external contract manufacturing organizations ("CMOs") to manufacture pegozafermin for our ongoing and planned clinical trials. While these trials are ongoing, we plan to work with our CMOs to optimize and scale-up the manufacturing process for pegozafermin to support the increased production that will be needed for later-stage clinical trials and commercialization, if pegozafermin is approved.
- **Establish a commercial infrastructure in key geographies**. We have worldwide rights to pegozafermin and intend to develop the sales infrastructure required for commercialization in the United States. We also plan to evaluate options, including strategic collaborations, for commercializing pegozafermin, if approved, in other key markets, such as Europe and China.

Our Focus on Liver and Cardio-Metabolic Disease

We are focused on developing and commercializing therapeutic interventions that have a clinically meaningful impact on patients with liver and cardio-metabolic diseases. These diseases, including NASH and SHTG, represent leading global causes of morbidity and mortality. Despite a wave of public health campaigns to promote better diet and exercise habits and a range of treatment options available for many of these diseases, there is a significant unmet medical need for more effective therapies to improve patient outcomes and reduce the burden on global healthcare systems.

We are currently developing our lead product candidate, pegozafermin, a specifically engineered glycoPEGylated analog of FGF21, for the treatment of NASH and SHTG. We believe pegozafermin is an ideal candidate for the treatment of NASH based on its ability to address the key liver pathologies in NASH, its ability to address the underlying metabolic dysregulation in NASH patients, its favorable tolerability profile, and its potential

for a longer dosing interval. Multiple epidemiological studies have linked NAFLD to increased cardiovascular disease, concluding that the majority of deaths among NAFLD patients are attributable to cardiovascular disease. As a result, we believe it is important that new therapeutics options for NASH address the underlying cardiovascular and metabolic dysregulations in these patients. We are also developing pegozafermin for the treatment of SHTG given the potential of pegozafermin to meaningfully reduce triglycerides. Pegozafermin may have a competitive differentiation from approved therapies and other molecules in development based on its impact on improving liver fat and other metabolic markers in addition to triglyceride reduction.

Disease Overview - NASH

NASH, a severe form of NAFLD, is characterized histologically by the additional presence of inflammation and hepatocellular injury such as visible ballooning and has a significantly worse prognosis, with the potential to progress to liver fibrosis, cirrhosis or HCC.

NASH represents a large and rapidly growing problem in the United States and worldwide. Diagnoses have been on the rise and are expected to increase dramatically in the next decade. The prevalence of NAFLD, which affects approximately 25% of the global population, and NASH, which develops in approximately 20% to 25% of NAFLD patients, is driven primarily by the worldwide obesity epidemic. As a result, the prevalence of NASH has increased significantly in recent decades, paralleling similar trends in the prevalence of obesity, insulin resistance and Type 2 diabetes. The prevalence of these conditions is expected to increase further in view of the unhealthy nutrition habits, such as consumption of a diet high in fructose, sucrose and saturated fats, and sedentary behavior that characterize modern lifestyle.

The critical pathophysiologic mechanisms underlying the development and progression of NASH include reduced ability to handle lipids, increased insulin resistance, injury to hepatocytes and liver fibrosis in response to hepatocyte injury. NASH patients have an excessive accumulation of fat in the liver resulting primarily from a caloric intake above and beyond energy needs. A healthy liver contains less than 5% fat, but a liver in someone with NASH can contain more than 20% fat. This abnormal liver fat contributes to the progression to NASH, a liver necro-inflammatory state, that can lead to scarring, also known as fibrosis, and, for some, can progress to cirrhosis and liver failure—cirrhosis develops in approximately 20% to 45% of patients. In some cases, cirrhosis progresses to decompensated cirrhosis, which results in permanent liver damage that can lead to liver failure. In addition, it is estimated that 8% of patients with advanced fibrosis will develop HCC. NASH is a complex, multifaceted disease that doesn't just affect the liver. Patients with NASH frequently have other significant metabolic co-morbidities such as obesity, hyperglycemia, dyslipidemia and systemic hypertension (a constellation of which is commonly referred to as metabolic syndrome) and these further contribute to the risk of cardiovascular disease.

Disease Overview - SHTG

We are also developing pegozafermin for the treatment of SHTG. Hypertriglyceridemia ("HTG") is characterized by elevated fasting plasma triglyceride levels > 200 mg/dL and SHTG is typically defined as triglyceride levels of ≥ 500 mg/dL. SHTG is associated with an increased risk of NAFLD, NASH and cardiovascular diseases, as well as acute pancreatitis, accounting for up to 10% of all acute pancreatitis episodes. A third-party study utilizing an omega-3 fatty acid ("omega-3 FA") demonstrated the linkage between a reduction in triglycerides and favorable cardiovascular clinical outcomes.

It is estimated that there are 4 million patients in the United States with triglyceride levels of ≥ 500 mg/dL of which approximately 800,000 patients are inadequately treated with existing therapies and are thereby at increased risk for acute pancreatitis and atherosclerotic cardiovascular events. Of these patients, it is estimated that up to 100% have clinically meaningful hepatic fat using magnetic resonance imaging – proton density fat factor ("MRI-PDFF") ≥ 5%; baseline data from the sub-study in ENTRIGUE; n=24), up to 70% have Type 2 diabetes, and up to 65% have high LDL. This patient population is expected to increase due to the triple epidemic of obesity, metabolic syndrome and Type 2 diabetes. In addition, the addressable market has the potential to expand as a result of increasing awareness of the importance of treating elevated triglyceride levels, similar to the focus today of physicians on managing LDL levels, as well as the commercial efforts of other companies that are expected to promote triglyceride reduction.

The treatment regimen for SHTG includes dietary restrictions and lipid-lowering drug treatment such as fibrates, omega-3 fish oils and niacin. Some statins are indicated in HTG but do not have an indication for use in SHTG. Despite multiple agents approved for the treatment of SHTG, these agents have limitations that may not make them ideal for all patients. In third-party studies, up to 50% of treated SHTG patients were unable to reduce their triglyceride levels to < 500 mg/dL despite using approved drugs and are considered refractory patients. These refractory patients have substantial unmet medical need and represent a significant market opportunity for pegozafermin as an add-on therapy along with the opportunity for pegozafermin to be used in patients not on any background therapy. Given the continuing unmet need in SHTG and limitations of current treatments, there are other novel agents in development for the treatment of SHTG, including ANGPTL3 and APOC3 inhibitors.

Diagnosis

Most people with NASH are asymptomatic and their disease is often discovered incidentally following a liver imaging procedure, such as an ultrasound, prescribed for other reasons or as part of an investigation for elevated liver enzymes. Once suspected clinically, a liver biopsy is required to definitively diagnose NASH, which necessitates the joint presence of steatosis, ballooning and lobular inflammation. Once pathologically confirmed, the severity of NAFLD and NASH is determined using the histologically validated NAS, which grades disease activity on a scale of 0 to 8. The NAS is the sum of the individual scores for steatosis (0 to 3), lobular inflammation (0 to 3), and hepatocellular ballooning (0 to 2) but does not include a score for fibrosis. Fibrosis staging (F0-F4) relies on the Kleiner classification (F0 = no fibrosis; F1 = perisinusoidal or periportal fibrosis (not both); F2 = both perisinusoidal and periportal fibrosis; F3 = bridging fibrosis; F4 = cirrhosis).

Histological diagnosis remains the gold standard for assessment of NASH and fibrosis. However, given that liver biopsy is associated with risks of pain, bleeding and other morbidity, as well as significant cost, the procedure is not practical for general patient screening. Additionally, histology diagnosis is confounded by evaluation of a small sliver of a large heterogenous organ that may not represent the full organ, and significant variability in reading of slides including inter- and intra-reader variability. Several non-invasive tools such as clinical risk scores, serum markers and imaging techniques are increasingly used to assess NASH patients. Non-invasive tests (“NITs”) such as the Fibroscan-AST (“FAST”) score, Fibrosis-4 index, the Enhanced Liver Fibrosis score and vibration-controlled transient elastography, (“VCTE”), have been validated and are increasingly used. These NITs have an excellent negative predictive value and an acceptable positive predictive value for detection of advanced (≥ F3) fibrosis and are increasingly used in clinical settings. Additionally, evidence is emerging that shows a correlation between reduction in steatosis as measured by MRI-PDFF and reduction in ALT ≥17 U/L and histologic improvement on liver biopsy. In draft guidance, the FDA encouraged sponsors to identify biochemical or noninvasive imaging biomarkers that, once characterized and agreed by the FDA, could replace liver biopsies for patient selection and efficacy assessment in clinical trials.

We expect that the validation and subsequent adoption of these NITs will result in an increase in the diagnosis and treatment rates for NASH in the future.

FGF21 Overview

Fibroblast growth factors (“FGFs”), including FGF21 and FGF19, are a large family of cell-signaling proteins involved in the regulation of many processes within the body. FGF21 is an endogenous metabolic hormone that regulates energy homeostasis, glucose-lipid-protein metabolism and insulin sensitivity, and modulates the pathways that mitigate against intracellular stress. FGF21 is secreted primarily by the liver but is also secreted by the white adipose tissue (“WAT”), skeletal muscle and the pancreas. FGF21 exerts its biological benefits through the activation of three fibroblast growth factor receptors (“FGFRs”), FGFR1c, FGFR2c and FGFR3c, and requires co-activation of the transmembrane protein cofactor beta Klotho (“ß-Klotho”). FGF21 is not believed to activate FGFR4, which has been associated with adverse effects. FGF21 can act directly or indirectly on target organs by mediating downstream regulators, such as adiponectin, and upstream regulators that induce FGF21, such as nutritional stress or transcription factors.

Biological Effects of FGF21:

Reducing Liver Steatosis by Improving Lipid Handling and Insulin Sensitivity

FGF21 has been clinically shown to reduce liver steatosis. FGF21 reduces liver steatosis by (1) increasing fatty acid oxidation in the liver, (2) reducing the deposition of free fatty acids from peripheral tissue to the liver and (3) reducing DNL in the liver. FGF21 exerts its systemic effects by reducing the serum levels of lipids (e.g., triglycerides, LDL cholesterol) and increasing insulin sensitivity. Increasing insulin sensitivity reduces lipolysis and can also reduce serum levels of lipids. In particular, FGF21 has been demonstrated to reduce liver fat in patients with NASH in multiple clinical trials.

Improving Liver Inflammation and Fibrosis

FGF21 is also believed to reduce liver fibrosis, the pathological change most clearly linked to liver-related morbidity in NASH patients via two potential pathways. One pathway is through the metabolic benefits of FGF21 described above. Long-term improvements in metabolic regulation reduce the ongoing liver injury that drives fibrosis and thus allows the liver time to heal. The other pathway is a direct anti-fibrotic effect mediated via adiponectin, an adipokine that is upregulated by FGF21. Increased adiponectin downregulates the hepatic stellate cells that are activated upon hepatic injury and responsible for collagen deposition and subsequent fibrosis. FGF21 demonstrated an improvement in liver fibrosis in patients in NASH in a clinical trial.

FGF21 Signaling

As noted above, FGF21 exerts its biological benefits through the co-activation of FGFRs and ß-Klotho. FGFRs are expressed widely throughout the body whereas ß-Klotho is primarily expressed in metabolic tissues such as adipose tissue, liver, and pancreas, thereby providing organ specificity to FGF21. The binding of FGF21 is a two-step process. The C-terminus of FGF21 initially binds to ß-Klotho enabling the N-terminus to form an expanded complex with one of the FGFRs. Once the co-receptor complex has formed with ß-Klotho and one of the FGFRs, a series of intracellular signaling cascades is initiated. These signaling cascades enable FGF21 to exert its biological functions.

FGF21 activates three specific FGFRs (FGFR1c, FGFR2c and FGFR3c), which based on nonclinical studies and clinical trials, appear to be responsible for mediating the desired therapeutic actions of FGF21 in NASH. FGF21 is not believed to activate FGFR4. Activation of FGFR4 results in an increase in LDL cholesterol and has been implicated in the etiology or progression of HCC.

Pegozafermin

Overview

We are developing pegozafermin, a specifically engineered glycoPEGylated analog of FGF21, for the treatment of NASH and SHTG. Pegozafermin has been specifically engineered to retain the activity of native FGF21 while extending its half-life. Specifically, it has been engineered to: (1) protect against proteolysis and reduce renal clearance, (2) have an extended half-life, (3) minimize susceptibility to aggregate in solution and (4) optimize its potency, enabling the potential use of lower dosage/doses. Additionally, we believe that pegozafermin may enhance binding affinity for ß-Klotho, by altering the conformation of the C-terminus which could have a positive impact on efficacy.

Primary Structure and Protein Engineering of Pegozafermin

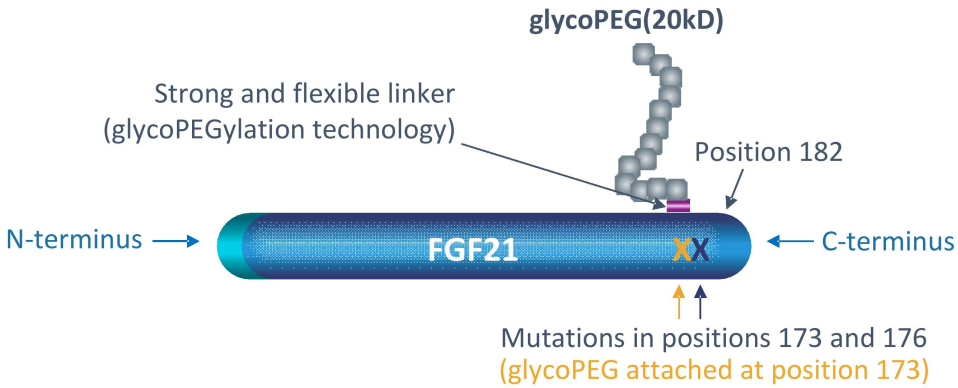
Pegozafermin has been optimally constructed with two mutations via substitutions with natural amino acids at site-specific positions (173 and 176) toward the C-terminus end of the hormone. The mutations were incorporated into the FGF21 sequence after existing proline to create a consensus sequence for glycosylation. Subsequently, the glycosyl linker and a single 20 kDa glycoPEG moiety were enzymatically introduced at the O-linked glycosylation consensus site (position 173) via the proprietary glycoPEGylation technology. Our glycoPEG moiety is an activated form of the PEG molecule with the use of Sialic Acid, CMP-SA-PEG. The proximity of the mutations ensures consistent and efficient attachment of the glycoPEG moiety.

Pegozafermin has two modified natural amino acid residues:

- S173T: Serine modified to Threonine at position 173; and
- R176A: Arginine modified to Alanine at position 176.

In addition, a Methionine residue was introduced at the N-terminus which acts as the translation initiation signal. Figure 1 below shows the structure of pegozafermin.

Figure 1: Structure of Pegozafermin



The increase in the size of the molecule from 19.4 kDa to 40 kDa together with the site-specific mutations adjacent to the primary cleavage site of FGF21 (by the FAP enzyme between positions 171 and 172 on the native amino acid chain, which would be represented by positions 172 and 173 in our molecule starting with Methionine in position 1) are designed to prolong the half-life of the molecule. Additionally, we believe that the use of glycoPEGylation technology produces a comparatively stronger and more flexible structure, which aids in the development of a stable formulation. PEGylation technology has been used successfully in many pharmaceutical products including products that have been marketed for more than 10 years. Similar moles of FGF21 are delivered with pegozafermin 30mg and efruxifermin 50mg.

Pegozafermin uses a proprietary glycoPEGylation technology that has been previously validated by a third party, as this technology is incorporated in another pharmaceutical product (Lonquex® by Teva) that has received regulatory approval and is currently commercialized in the European Union.

Figure 2: Summary of Pegozafermin Attributes and Benefits

Features	Description	Potential Benefit
Use of PEG (via glycoPEGylation)	▪ Increases protein size and hydrodynamic volume that reduces renal filtration ▪ Prevents degradation by endocytosis and proteolytic enzymes	▪ Prolongs half-life
	▪ Protects antigenic sites present on the protein surface (i.e. antigenic epitopes)	▪ Reduces immunogenicity
	▪ Steric repulsion between the PEGylated surfaces increases water solubility and reduces aggregates	▪ Results in more stable formulation
Site-Specific Mutations	▪ Mutation at position 173 is immediately adjacent to the primary cleavage (FAP enzyme) site of FGF21	▪ Prolongs half-life
GlycoPEGylation Technology	▪ Allows site specific linkage (glycoPEG moiety to position 173) ▪ Proximity of the glycoPEG moiety to the C-terminus induces conformational changes to the molecule	▪ Retains potency against receptor to improve efficacy
	▪ Provides a strong and flexible glycosyl bond that helps the glycoPEG moiety to remain intact, further reducing degradation	▪ Further enhances half-life

Therapeutic Potential of Pegozafermin Supported by Preclinical Animal Models of NASH, Diabetes and Obesity

Pegozafermin has been evaluated in three animal models of direct relevance to NASH. These included: (1) Stelic Animal Model, ("STAM"), (2) Diet-induced NASH ("DIN") model and (3) spontaneous diabetic obese cynomolgus monkey model. Additional studies done in diabetes mouse model and diet induced obesity mouse model showed benefits in key markers of relevance in NASH.

A wide range of doses were tested in these studies as well as weekly and once every two-week dosing regimen was tested in a cynomolgus monkey study. The key outcomes of these studies are summarized in Figure 3 below.

Figure 3: Summary of NASH Pharmacology Studies

Preclinical pharmacology study with pegozafermin	Improved Insulin Sensitivity	Improved Triglycerides and Cholesterol	Reduced Hepatocyte Injury	Reduced Liver Steatosis, Inflammation & Fibrosis	Body Weight Reduction
DIN mouse model I (10 weeks)	✓	✓	✓	✓	✓
DIN mouse model II (19 weeks)	✓	✓	✓	✓	✓
Diabetic obese cynomolgus monkey study 1 (8 weeks; weekly dosing)	✓	✓	✓	Not evaluated	✓
Diabetic obese cynomolgus monkey study 2 (4 weeks; QW or Q2W dosing)	✓	✓	✓	Not evaluated	✓

✓ Statistically significant benefit observed.

Pegozafermin Clinical Development in NASH

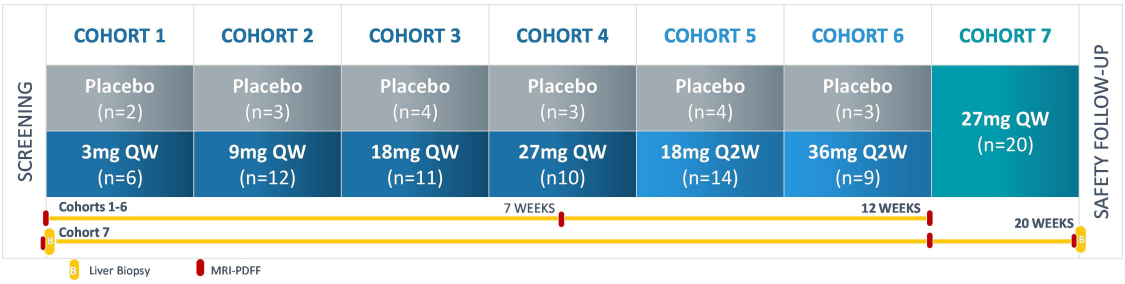
Phase 1a Clinical Trial of Single-Dose of Pegozafermin in Healthy Volunteers

We conducted a Phase 1a clinical trial to evaluate the safety, tolerability and pharmacokinetics ("PK") of pegozafermin in 58 healthy volunteers. In this randomized, double-blind, placebo-controlled, Phase 1a, first-in-human, SAD clinical trial the PK profile of pegozafermin was generally dose-proportional or slightly more than dose-proportional with a half-life of approximately 55 to 100 hours. At single doses of 9.1 mg and higher, significant improvements were observed in key lipid parameters measured at Day 8 and Day 15 after dosing on Day 1. The mean changes versus baseline include significant reductions in triglycerides (up to 51%) and LDL-C (up to 37%) and increase in HDL-C (up to 36%) despite the baseline values being in the normal range. Pegozafermin demonstrated rapid (starting from Day 2), sustained and durable improvements on lipid parameters for two weeks or more after single-dose administration. Pegozafermin was well tolerated across the dose range and there were no deaths, serious adverse events or discontinuations due to adverse events. The most commonly observed treatment-related adverse events, occurring in at least two subjects in the pooled pegozafermin group, were injection site reactions and headache, all of which were reported as mild. No clinically meaningful trends were observed in gastrointestinal events, laboratories or vital signs including blood pressure or heart rate changes.

Phase 1b/2a Proof of Concept Clinical Trial in NASH Patients

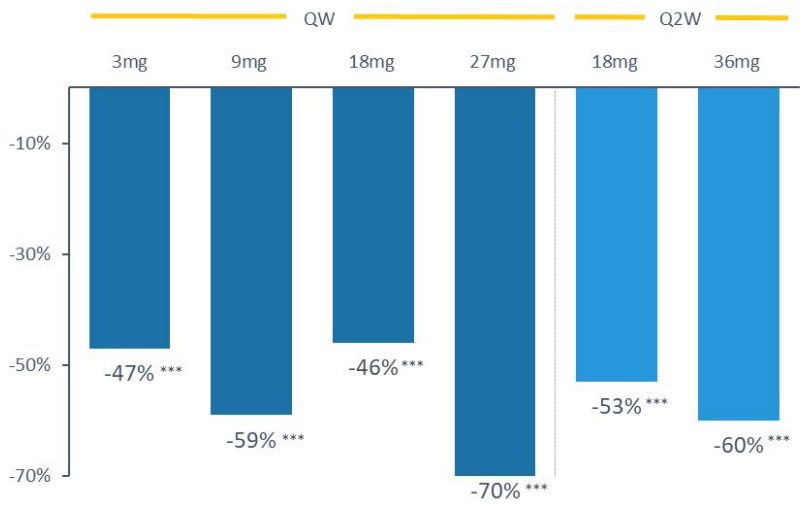
In 2020 and 2022, we presented positive topline results from cohorts 1 to 6 and cohort 7, respectively, in our Phase 1b/2a trial in NASH patients which has informed the advancement of our clinical strategy in NASH. The Phase 1b/2a trial for cohorts 1 to 6 was multicenter, randomized, double-blind, placebo-controlled, multiple ascending dose-ranging and enrolled a total of 81 patients to receive weekly (3 mg/9 mg/18 mg/27 mg) or every two-week (18 mg/36 mg) dosing of pegozafermin or placebo for up to 12 weeks. Key endpoints assessed were safety, tolerability, and PK of pegozafermin as well as change in liver fat measured by MRI-PDFF and other metabolic markers. Cohort 7 was an open label cohort that enrolled 20 patients who received weekly dosing of pegozafermin at 27 mg for 20 weeks. Key endpoints assessed were changes in histology from baseline, liver fat changes from baseline and safety and tolerability. The trial design is shown in Figure 4 below.

Figure 4: Phase 1b/2a Trial Design



As shown in Figure 5 below, all dose groups in cohorts 1 to 6 demonstrated significant reductions in liver fat at week 13, with relative reductions up to 60% versus baseline and up to 70% versus placebo, as measured by MRI-PDFF. 43% of the patients at the highest dose achieved normal liver fat content of < 5%. A significant proportion of patients responded to therapy with up to 88% and 71% of patients achieving a ≥ 30% or a ≥ 50% reduction in liver fat versus baseline, respectively.

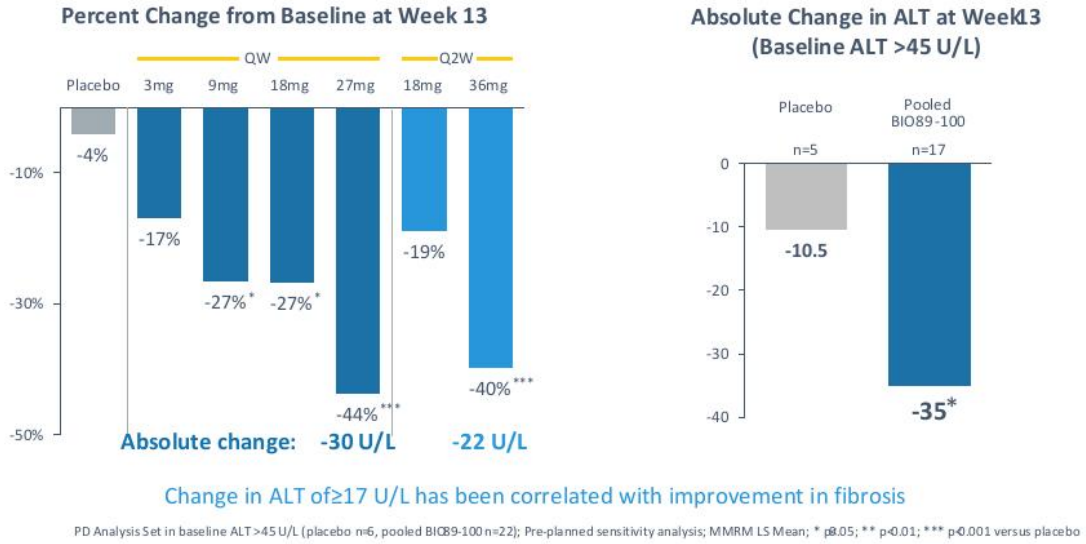
Figure 5: Relative Reduction in Liver Fat vs. Placebo at Week 13



MRI Analysis Set; MMRM LS Mean; * p<0.05; ** p<0.01; *** p<0.001 versus placebo

As shown in Figure 6 below for cohorts 1 to 6, treatment with pegozafermin also resulted in significant improvements in liver transaminases, with up to a 44% reduction in ALT and a 35 U/L decrease in ALT in patients with elevated baseline levels. Treatment with pegozafermin resulted in significant reductions in triglycerides (up to 28%; $p<0.05$), non-HDL (up to 16%; $p<0.01$) and LDL-C (up to 16%; $p<0.05$). Triglycerides were reduced to a greater extent in patients with elevated triglycerides at baseline (TG ≥ 200 mg/dL), and 53% of the pegozafermin patients in this group normalized triglyceride levels versus 0% in the placebo group. Pegozafermin also demonstrated significant increases in the insulin-sensitizing hormone adiponectin (up to 61%; $p<0.001$). Improvements were also noted across the spectrum of metabolic marker data vs. placebo for the 27 mg QW dose group including HOMA-IR, glucose, HbA1c, and body weight ($p<0.05$).

Figure 6: Clinically Meaningful ALT Reduction; Greater Reduction in Patients with High ALT



Additional analyses demonstrated that pegozafermin treatment resulted in significant reductions in liver volume of up to 15% and liver fat volume of up to 65% in treated patients at 13 weeks compared to baseline, as measured by MRI-PDFF. A post-hoc analysis presented at The Liver Meeting of AASLD in November 2021 assessed the effect of pegozafermin on spleen volume (SV) in NASH patients without advanced fibrosis. SV was evaluated by MRI in all eligible patients on pegozafermin 27 mg every week dose (n=8), pegozafermin 36 mg every two-week dose (n=8) and 16 patients on placebo. At baseline, it was observed that SV was correlated with liver volume, vibration-controlled transient elastography (VCTE) score and body mass index (BMI), and negatively correlated with platelet count. Findings at study Day 50 and Day 92 demonstrated that treatment with pegozafermin led to a progressive and significant decrease in SV compared to placebo (on Day 50, treated patients saw an average 7.4% decrease in SV and by Day 92 patients saw an average 11.8% decrease in SV).

Paired-biopsy, Open-label Histology Cohort (Cohort 7)

Cohort 7 in the Phase 1b/2a trial was a single-arm cohort that enrolled 20 patients with biopsy-confirmed fibrosis stage F2 and F3 NASH who were treated once weekly for 20 weeks with 27 mg of pegozafermin. 19 of 20 patents received an end of treatment biopsy and one patient withdrew consent. A greater than or equal to 2-point improvement in NAS (with 1-point from either ballooning or inflammation) and no worsening of fibrosis was the nominal primary endpoint. Key secondary endpoints included response rates on NASH resolution without worsening of fibrosis, improvement in at least one stage of fibrosis without worsening NAS and safety/tolerability. Patients had a mean BMI of 37 and type 2 diabetes was prevalent in most patients. 65% had fibrosis stage F3 NASH and 35% had fibrosis stage F2 NASH. The baseline values for VCTE, ProC3, and transaminases were consistent with a more advanced population.

74% of patients achieved a greater than or equal to 2-point improvement in NAS with at least a 1-point improvement in ballooning or inflammation. Substantial reductions were observed across all 3 NAS components (≥1 point change) – ballooning (79%), inflammation (47%), and steatosis (74%). All patients had improvement or no change in ballooning and inflammation. The histology results demonstrate proof-of-concept for the translation of pegozafermin's effects on liver fat, ALT, and other relevant non-invasive measures into histological improvement.

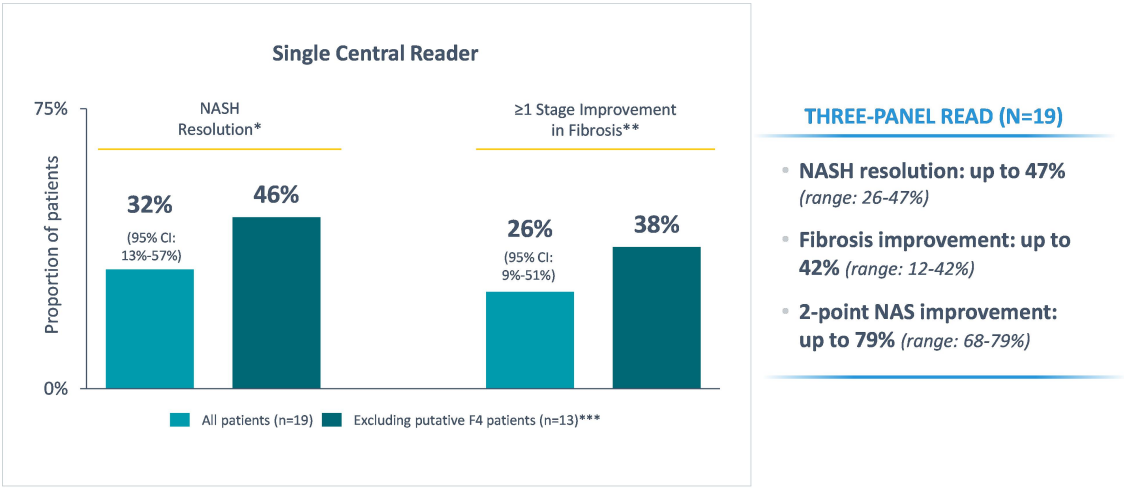
Figure 7: Histology Results

≥2-point improvement in NAS without worsening of fibrosis[1] (primary endpoint)	63%
≥2-point improvement in NAS[1]	74%
NASH resolution without worsening of fibrosis	32%; 95% CI: 13%-57%
One-stage improvement of fibrosis without worsening of NASH	26%; 95% CI: 9%-51%
NASH resolution or fibrosis improvement	47%

NAS = NAFLD Activity Score
[1]A 2-point improvement in NAS score required a 1-point improvement in either ballooning or inflammation

Data from a new analysis of the same histology slides by a panel of an additional three expert liver pathologists resulted in a wide range of response rates, with rates of NASH resolution without worsening of fibrosis up to 47% (range: 26%-47%) and rates of ≥ 1-stage improvement in fibrosis without worsening of NASH up to 42% (range: 12%-42%). This three-reader panel scored six of the nineteen patients as having F4 fibrosis at baseline (putative F4), which was an exclusion criterion for the Phase 1b/2a trial. Excluding the putative F4 patients (n=6) resulted in a higher proportion of patients meeting the registration enabling histological endpoints compared to the primary analysis based on the single central reader, as shown in Figure 8 below.

Figure 8: New Analysis of Cohort 7 Histology Slides By a Panel of Three Experts



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*and no worsening of fibrosis **and no worsening of NASH
*** In the post-hoc exploratory analyses, a panel of three additional expert NASH pathologists assessed the same baseline (BL) and end of treatment (EOT) slides that had been evaluated by the central pathologist. Slides from BL and EOT were mixed and the three-reader pathologist panel were blinded to the timepoint; they scored 6/19 patients as having F4 fibrosis at baseline (putative F4)

Pegozafermin also demonstrated beneficial effects in the subset of patients with F4 stage fibrosis as shown in Figure 9 below.

Figure 9: Pegozafermin Effects in Fibrosis Stage F4 Patients

Parameter (Mean or %)	Putative F4 fibrosis (n=6)*
LIVER STEATOSIS	
Relative liver fat reduction by MRI-PDFF (%)	- 71%
MRI-PDFF 30%/50% responders	100%/100%
LIVER TRANSAMINASES	
Percent change in ALT	- 51%
Percent change in AST	- 49%
INSULIN SENSITIVITY	
Percent change in adiponectin	99%
NON-INVASIVE MARKERS OF FIBROSIS	
Change in VCTE score (kPa)/VCTE responders***	-3.8** / 60%**
Change in FAST score/ FAST responders***	-0.5** / 100%**

*Patients assessed with F4 fibrosis by 2+ panel pathologists
**N=5; one outlier with poor quality measurement was excluded.
***VCTE >20% reduction; FAST score ≤0.35.

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- Fibrosis improvement ≥1 stage without worsening of NASH: **17-57%**
- NASH resolution without worsening of fibrosis: **20-50%**

To assess pegozafermin's effect on the whole liver, a number of NITs including imaging, serum biomarkers, and risk stratification scores were built into the study. Clinically meaningful and significant changes were observed across these key NITs associated with fibrosis, risk of fibrosis, or NASH resolution. The consistency of data across all these endpoints and the magnitude of changes observed in these NITs suggest that pegozafermin is improving total liver health.

Figure 10: Non-Invasive Tests (NITs) [marker of]

	Mean change from baseline at Week 20	**Responder rates by clinically relevant thresholds**
MRI-PDFF [liver fat content][1]	-64%***	100%/78% [≥ 30%/≥ 50%]
ALT (Alanine aminotransferase) [liver damage][2]	-46%***	71%[3] [≥ 17 U/L]
FAST Score [risk for advanced fibrosis][4]	-76%***	88% [≤ 0.35]
VCTE [liver stiffness][5]	-31%***	72% [> 20% decrease]
Pro-C3 [collagen deposition][6]	-20%***	63% [> 15% decrease]

*** p<0.001
1 Changes from baseline ≥ 30% and ≥ 50% have been correlated with NASH improvement
2 ALT changes ≥ 17 U/L have been correlated with histological improvement
3 In patients with elevated ALT as defined by ≥ 30 U/L in women and ≥ 40 U/L in men (n=14)
4 FAST score is a composite of imaging and blood markers and measured on 0-1 scale, a score ≤ 0.35 predicts Fibrosis Stage F0/F1 and NAS < 4
5 VCTE is a Fibroscan assessment, > 20% reduction has been correlated with fibrosis improvement
6 Pro-C3 is a blood-based measurement, > 15% reduction has been correlated with fibrosis improvement

In addition to significant improvement in liver health, treatment with pegozafermin also had significant positive effects on glycemic control, lipids, adiponectin, and body weight.

Figure 11: Cardio-Metabolic Endpoints

	Mean change from baseline at Week 20
HbA1c absolute change[1]	-0.9%**
Triglycerides[2]	-32%***
LDL-C	-13%*
HDL-C	+23%***
Adiponectin	+88%***
Body Weight	-4%***

*p<0.05; **p<0.01; ***p<0.001

[1] In patients with HbA1c ≥ 6.5% at baseline (n=10); patients were all on concomitant diabetes medications

[2] In patients with elevated triglycerides at baseline (n=11); reduction was -26% across total population

In 83 patients treated with pegozafermin across the full Phase 1b/2a trial in cohorts 1 to 7, pegozafermin continues to be generally well tolerated with a favorable safety profile. There have been no drug-related serious adverse events and only one treatment-related discontinuation. Pooled pegozafermin treatment related adverse events in greater than or equal to 10% of patients were increased appetite (13% vs 0% placebo), diarrhea (13% vs 11% placebo), and nausea (12% vs 11% placebo). Most of the GI adverse events were mild and of short duration. A few mild injection site reactions were reported and there were no tremors and no hypersensitivity adverse events observed. Pegozafermin had no adverse effects on blood pressure or heart rate.

Phase 2b (ENLIVEN) Trial in Fibrosis Stage 2 or 3 NASH Patients

ENLIVEN is a multicenter, randomized, double-blind, placebo-controlled Phase 2b trial in biopsy-confirmed NASH patients with fibrosis stage 2 or 3 and NAS ≥ 4. The trial enrolled a total of 219 patients who receive either a weekly dose (15 mg or 30 mg) or an every two-week dose (44 mg) of pegozafermin in a liquid formulation or placebo for 24 weeks with a randomization schema of 4: 4: 2.5: 1 (placebo: 30 mg QW: 44 mg Q2W: 15 mg QW). All patients will continue treatment in a blinded extension phase for 24 weeks for a total treatment period of 48 weeks, with some of the placebo patients re-randomized to receive pegozafermin in the extension phase. The primary analysis will evaluate the effect of pegozafermin on the two FDA approvable histology endpoints 1-point fibrosis improvement with no worsening of NASH and NASH resolution with no worsening of fibrosis and will include patients who met histologic entry criteria F2/F3 patients and NAS ≥ 4 based on the three-panel consensus read of biopsies at baseline to ensure consistency between baseline and end of treatment biopsy reading methods. This three-panel consensus read was instituted after receipt of data from the expansion cohort of the Phase 1b/2a trial (cohort 7) to address biopsy reading variability and increase the likelihood of showing the true benefit of pegozafermin while maintaining adequate study power. Prior to this change, biopsy entry criteria for ENLIVEN was based on a single reader. We expect to report topline data in March 2023.

Pegozafermin Clinical Development in SHTG

In June 2022 we reported positive topline results from the ENTRIGUE Phase 2 trial of pegozafermin in SHTG patients. ENTRIGUE was a randomized, double-blind, placebo-controlled trial that enrolled a total of 85 SHTG patients either on stable background therapy (55% - statin/statin combos, and/or prescription fish oil, and/or fibrates) or not on any background therapy treated weekly (9 mg, 18 mg or 27 mg) or every two weeks (36 mg) with pegozafermin or placebo over an eight-week treatment period. The trial enrolled an advanced population of patients with high risk of cardiovascular disease as evidenced by mean baseline values of treated patients with TGs of 733 mg/dL, non-HDL-C of 211 mg/dL, 43.5% with HbA1c ≥ 6.5%, and liver fat content of 20.1%. The primary endpoint was the percentage change in fasting triglyceride levels from baseline.

As shown in Figure 12 below, results demonstrated statistically significant reductions in median triglycerides from baseline across all dose groups treated with pegozafermin compared to placebo after 8 weeks. Additionally, as shown in Figure 13 below, results were consistent in patients not on background therapy or on background therapy (consistent results on statins or statin combos, prescription fish oils, and fibrates) and across various subgroups, including those with the greatest disease burden, such as Type 2 diabetes and baseline TG levels ≥ 750 mg/dL.

Figure 12: Median Percent Change in Triglycerides from Baseline at Week 8

Dosing group	Median TG reduction
Placebo (n=18)	-12%
9 mg QW (n=16)	-57%***
18 mg QW (n=17)	-56%***
27 mg QW (n=18)	-63%***
36 mg Q2W (n=16)	-36%*

* p<0.05; *** p<0.001 versus placebo based on Wilcoxon Rank-Sum Test

Figure 13: Median Percent Change in Triglycerides from Baseline at Week 8

Dosing group	Patients on background therapy[1]	Patients not on background therapy
Placebo	-18%	5%
9 mg QW	-59%	-50%
18 mg QW	-56%	-59%
27 mg QW	-68%	-62%
36 mg Q2W	-45%	-21%

1. Background therapy defined as concomitant lipid modifying therapy
Patients on background therapy: placebo (n=11), 9 mg QW (n=8), 18 mg QW (n=9), 27 mg QW (n=10), 36 mg Q2W (n=8)
Patients not on background therapy: placebo (n=6), 9 mg QW (n=8), 18 mg QW (n=8), 27 mg QW (n=6), 36 mg Q2W (n=8)

Responder analysis on primary endpoint of TG reduction demonstrated:

- A significantly higher proportion of patients reached the initial treatment goal of reducing TG < 500 mg/dL on pooled pegozafermin vs. placebo (80% vs. 29%; p<0.001).
- Treatment with 27 mg QW resulted in a significantly higher proportion of patients achieving TG normalization (< 150 mg/dL) vs. placebo (31% vs. 0%; p<0.05) and
- Greater proportion of patients achieved significant TG reduction of ≥ 50% from baseline vs. placebo (75% vs. 6%; p<0.001).

Pegozafermin treatment also resulted in significant improvements compared to placebo (mean percent change from baseline) and clinically meaningful changes on an absolute basis in non-HDL-C and apo B that are key markers of cardiovascular risk (absolute change from baseline of 55 mg/dL and 22 mg/dL in non-HDL-C and apo B respectively with 27 mg QW dose). As shown in Figure 14 below, patients treated across all doses with pegozafermin also demonstrated an improvement in HDL-C and no change in LDL-C vs. placebo.

Figure 14: Mean Percent Change in non-HDL-C and apo B from Baseline at Week 8

Dosing group	non-HDL-C	apo B
Placebo	-3%	-1%
9 mg QW	-14%	-11%
18 mg QW	-22%**	-14%*
27 mg QW	-29%***	-18%**
36 mg Q2W	-9%	-1%

* p<0.05; ** p<0.01; *** p<0.001 versus placebo based on MMRM analysis

Pegozafermin treatment resulted in a mean relative reduction in liver fat from baseline at week 8 across all dose groups versus placebo in the sub-study of patients with MRI-PDFF. The results are summarized in Figure 15 below.

Figure 15: Mean Relative Reduction in Liver Fat vs. Baseline at Week 8 in Sub-study

Dosing group	**MRI-PDFF**
Placebo (n=6)	-5%
9 mg QW (n=3)	-55%*
18 mg QW (n=5)	-38%
27 mg QW (n=7)	-44%
36 mg Q2W (n=2)	-37%

* p<0.05 versus placebo based on ANCOVA analysis

- A significant proportion of patients responded to therapy with up to 88% and 41% of treated patients vs. 0% of placebo patients achieving a ≥ 30% or a ≥ 50% reduction in liver fat versus baseline, respectively.
- Results also demonstrated a significant reduction in liver enzymes and an improvement in glycemic control markers in pegozafermin treated patients.

Pegozafermin continues to be generally well tolerated with a favorable safety profile across doses consistent with prior studies. In ENTRIGUE, the most commonly reported treatment-related adverse events were nausea, diarrhea and injection site reactions, all which were classified as mild or moderate. No tremors or transaminase elevation adverse events were observed. There were no drug-related serious adverse events and two Grade 2 treatment-related discontinuations.

We received feedback from the FDA supporting the advancement of pegozafermin into Phase 3. The FDA agreed that the pre-clinical and clinical data package support the advancement of pegozafermin into Phase 3 with the proposed primary endpoint of reduction in triglycerides from baseline without the need for a clinical outcome study. The FDA also agreed to the proposed doses and proposed secondary endpoints and were generally aligned with other trial parameters. Since SHTG is a common, chronic condition and pegozafermin is a novel investigational biologic therapy, the agency recommended conducting two Phase 3 trials in SHTG, each of one year duration as part of the efficacy and safety database required to support the registration package. We have incorporated the agency's feedback into our protocol and plan to initiate the first of two recommended Phase 3 trials in SHTG in the second quarter of 2023. The primary endpoint in the planned Phase 3 trials is anticipated to be assessed at week 26.

Agreements with Teva

Agreements Relating to FGF21 Program

In April 2018, we entered into an Asset Transfer and License Agreement (the "FGF21 Agreement") with Teva Pharmaceutical Industries Ltd ("Teva"), under which we acquired certain patents, intellectual property and other assets relating to Teva's glycoPEGylated FGF21 program. Under this agreement, Teva also granted a perpetual, non-exclusive (but exclusive as to pegozafermin), non-transferable, worldwide license to patents and know-how related to glycoPEGylation technology for use in the research, development, manufacture and commercialization of the compound pegozafermin and products containing pegozafermin. In addition, we entered into a Sublicense Agreement with ratiopharm (the "ratiopharm Sublicense"), under which we were granted a perpetual, exclusive, worldwide sublicense to patents and know-how related to glycoPEGylation technology used in the development, manufacture and commercialization of pegozafermin and products containing pegozafermin.

Under the FGF21 Agreement, we are obligated to use commercially reasonable efforts to develop and commercialize pegozafermin in each of the United States and five major European countries. We have the right to sublicense all rights licensed to us by Teva under the FGF21 Agreement.

Pursuant to the FGF21 Agreement and the FASN Agreement (as defined and described below), we paid Teva a nonrefundable upfront payment of $6.0 million. In addition, under the FGF21 Agreement, we are required to make certain payments to Teva totaling $2.5 million for the achievement of certain clinical development milestones, and additional payments totaling up to $65.0 million upon achievement of certain commercial milestones. We are also obligated to pay Teva tiered royalties at percentages in the low-to-mid single-digits on worldwide net sales of products containing pegozafermin. Our royalty obligations will terminate, on a product-by-product and country-by-country basis, at the later of: (1) the date of expiration of the last to expire valid claim in the assigned patents that covers pegozafermin in such country, (2) the expiration of data or regulatory exclusivity for pegozafermin in such country and (3) 10 years from the first commercial sale of pegozafermin in such country. We are not required to make any payments to ratiopharm pursuant to the ratiopharm Sublicense.

The term of the FGF21 Agreement will continue, on a product-by-product and country-by-country basis, until the royalty term with respect to pegozafermin in such country expires. The ratiopharm Sublicense will continue until terminated in accordance with its terms. We may terminate the FGF21 Agreement and the ratiopharm Sublicense for any reason. Either party may terminate the FGF21 Agreement for cause for the other party's uncured material breach. ratiopharm may terminate the ratiopharm Sublicense for certain material breaches by us. Either party may terminate the FGF21 Agreement or the ratiopharm Sublicense in the event of bankruptcy of the other party. Teva may terminate the FGF21 Agreement if we challenge the validity of any patent licensed to us under the FGF21 Agreement. Termination of the FGF21 Agreement or the ratiopharm Sublicense will impact our rights under the intellectual property licensed to us by Teva and ratiopharm, respectively, but will not affect our rights under the assets assigned to us.

In April 2018, we also entered into a Reagent Supply and Technology Transfer Agreement, under which Teva supplied us with certain reagents required for the glycoPEGylation process that are necessary for our development and commercialization of pegozafermin, and transfer to us certain know-how required for the production of such reagents. This agreement expired in accordance with its terms on December 31, 2022. We transferred the manufacturing of such reagents to new suppliers prior to the end of 2022.

FASN Agreements

In April 2018, we entered into an Asset Transfer and License Agreement with Teva under which we acquired from Teva patents, intellectual property and other assets relating to Teva's development program of small molecule inhibitors of FASN (the "FASN Agreement"). Under the FASN Agreement we are obligated to use commercially reasonable efforts to develop and commercialize FASN in the United States and five major European countries. We have the right to sublicense all rights licensed to us by Teva under the FASN Agreement.

Pursuant to the FASN Agreement and the FGF21 Agreement (as described above), we paid Teva a nonrefundable upfront payment of $6.0 million. In addition, under the FASN Agreement, we are required to make certain payments to Teva totaling $2.5 million for the achievement of certain clinical development milestones, and additional payments totaling up to $65.0 million upon achievement of certain commercial milestones. We are also obligated to pay Teva tiered royalties at percentages in the low-to-mid single-digits on worldwide net sales of products arising from the FASN program. Our royalty obligations will terminate, on a product-by-product and country-by-country basis, at the later of: (1) the date of expiration of the last to expire valid claim in the assigned patents that covers FASN in such country, (2) the expiration of data or regulatory exclusivity for such product arising from the FASN program in such country and (3) 10 years from the first commercial sale of a product arising from the FASN program in such country.

The term of the FASN Agreement will continue, on a product-by-product and country-by-country basis, until the royalty term with respect to the product arising from the FASN program in such country expires. We may terminate the FASN Agreement for any reason. Either party may terminate the agreement for cause for the other party's uncured material breach, or in the event of bankruptcy of the other party.

Government Regulation and Product Approval

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

The process required by the FDA before biologic product candidates may be marketed in the United States is expensive and time-consuming. Generally, this process involves completing pre-clinical laboratory studies before the FDA will allow human clinical trials to commence. We are then required to complete human clinical trials to demonstrate that a product candidate is safe and effective. Following the completion of these clinical trials, we are required to prepare and submit a biologics license application ("BLA"), which presents the FDA with detailed clinical and safety data, as well as manufacturing data. As part of the review of a BLA, the FDA may inspect manufacturing facilities to assure the facilities, methods and controls are adequate to preserve the biological product's continued safety, purity and potency, and may also inspect selected clinical investigation sites to assess compliance with current Good Clinical Practices ("cGCP"). This process takes many years from inception through filing of a BLA application and the likelihood of success is highly uncertain.

Preclinical and Clinical Development

Prior to beginning the first clinical trial with a product candidate, we must submit an investigational new drug ("IND") application to the FDA. An IND is a request for authorization from the FDA to administer an investigational new drug product to humans. The central focus of an IND submission is the general investigational plan and the protocol(s) for clinical studies. Submission of an IND 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 cGCPs, which include the requirement that all research subjects provide their informed consent for their participation in any clinical study. Furthermore, an independent review board ("IRB") for each site proposing to conduct the clinical trial must review and approve the plan for any clinical trial and its informed consent form before the clinical trial begins at that site, and must monitor the study until completed. Regulatory authorities, the IRB or the sponsor may suspend a clinical trial at any time on various grounds, including a finding that the subjects are being exposed to an unacceptable health risk or that the trial is unlikely to meet its stated objectives.

For purposes of BLA approval, human clinical trials are typically conducted in three sequential phases that may overlap.

- ***Phase 1***—The investigational product is initially introduced into healthy human subjects or patients with the target disease or condition. These studies are designed to test the safety, dosage tolerance, absorption, metabolism and distribution of the investigational product in humans, the side effects associated with increasing doses, and, if possible, to gain early evidence on effectiveness.
- ***Phase 2***—The investigational product is administered to a limited patient population with a specified disease or condition to evaluate the preliminary efficacy, optimal dosages and dosing schedule and to identify possible adverse side effects and safety risks. Multiple Phase 2 clinical trials may be conducted to obtain information prior to beginning larger and more expensive Phase 3 clinical trials.
- ***Phase 3***—The investigational product is administered to an expanded patient population to further evaluate dosage, to provide statistically significant evidence of clinical efficacy and to further test for safety, generally at multiple geographically dispersed clinical trial sites. These clinical trials are intended to establish the overall risk/benefit ratio of the investigational product and to provide an adequate basis for product approval.

Concurrent with clinical trials, companies must finalize a process for manufacturing the product in commercial quantities in accordance with current good manufacturing practices ("cGMP") requirements. The manufacturing process must be capable of consistently producing quality batches of the product candidate and, among other things, must develop methods for testing the identity, strength, quality and purity of the final product, or for biologics, the safety, purity and potency.

BLA Submission and Review

Assuming successful completion of all required testing in accordance with all applicable regulatory requirements, the results of product development, nonclinical studies and clinical trials are submitted to the FDA as part of a BLA requesting approval to market the product for one or more indications. The submission of a BLA requires payment of a substantial application user fee to FDA, unless a waiver or exemption applies.

Once a BLA has been submitted, the FDA's goal is to review standard applications within ten months after it accepts the application for filing, or, if the application qualifies for priority review, six months after the FDA accepts the application for filing. In both standard and priority reviews, the review process may be extended by FDA requests for additional information or clarification. The FDA reviews a BLA to determine, among other things, whether a product is safe, pure and potent and the facility in which it is manufactured, processed, packed, or held meets standards designed to assure the product's continued safety, purity and potency. The FDA may convene an advisory committee to provide clinical insight on application review questions. Before approving a BLA, the FDA will typically inspect the facility or facilities where the product is manufactured. The FDA will not approve an application unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. Additionally, before approving a BLA, the FDA will typically inspect one or more clinical sites to assure compliance with cGCP. If the FDA determines that the application, manufacturing process or manufacturing facilities are not acceptable, it will outline the deficiencies in the submission and often will request additional testing or information. Notwithstanding the submission of any requested additional information, the FDA ultimately may decide that the application does not satisfy the regulatory criteria for approval.

After the FDA evaluates a BLA and conducts necessary inspections, the FDA may either issue an approval letter or a Complete Response letter. An approval letter authorizes commercial marketing of the product with specific prescribing information for specific indications. A Complete Response letter will describe deficiencies that the FDA has identified in the BLA. The FDA may delay or refuse approval of a BLA if applicable regulatory criteria are not satisfied, require additional testing or information and/or require post-marketing testing and surveillance to monitor safety or efficacy of a product.

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

Expedited Programs for Serious Conditions

The FDA maintains several programs intended to facilitate and expedite development and review of new drugs and biologics to address unmet medical needs in the treatment of serious or life-threatening diseases or conditions. These programs include Fast Track designation, Breakthrough Therapy designation, Priority Review and Accelerated Approval. These programs can significantly reduce the time it takes for the FDA to review a BLA, but they do not guarantee that a product will receive FDA approval. Even if a product qualifies initially, the FDA may later decide that the product no longer meets the conditions for qualification or decide that the time period for FDA review will not be shortened. The Consolidated Appropriations Act 2023 strengthens the FDA's authority to require and regulate post-approval studies of accelerated approval drugs and to expedite the rescission of accelerated approval based on these post-approval studies.

Post-Approval Requirements

Any products manufactured or distributed pursuant to FDA approvals are subject to pervasive and continuing regulation by the FDA, including, among other things, requirements relating to record-keeping, reporting of adverse experiences, periodic reporting, product sampling and distribution, and advertising and promotion of the product. After approval, most changes to the approved product, such as adding new indications or other labeling claims, are subject to prior FDA review and approval. Biologic 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. Changes to the manufacturing process are strictly regulated, and, depending on the significance of the change, may require prior FDA approval before being implemented. FDA regulations also require investigation and correction of any deviations from cGMP and impose reporting requirements upon companies and third-party manufacturers. 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, among other potential consequences.

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

Biosimilars and Reference Product Exclusivity

The Patient Protection and Affordable Care Act, as amended (collectively, the "Affordable Care Act") includes a provision called the Biologics Price Competition and Innovation Act of 2009 ("BPCIA"), which created an abbreviated approval pathway for biological products that are biosimilar to or interchangeable with an FDA-approved reference biological product.

Biosimilarity, which requires that there be no clinically meaningful differences between the biological product and the reference product in terms of safety, purity and potency, can be shown through analytical studies, animal studies, and a clinical study or studies.

Under the BPCIA, an application for a biosimilar product may not be submitted to the FDA until four years following the date that the reference product was first licensed by the FDA. In addition, the approval of a biosimilar product may not be made effective by the FDA until 12 years from the date on which the reference product was first licensed. During this 12-year period of exclusivity, another company may still market a competing version of the reference product if the FDA approves a full BLA for the competing product containing that applicant's own preclinical data and data from adequate and well-controlled clinical trials to demonstrate the safety, purity and potency of its product. At this juncture, it is unclear whether products deemed "interchangeable" by the FDA will, in fact, be readily substituted by pharmacies, which are governed by state pharmacy law.

The BPCIA is complex and continues to be interpreted and implemented by the FDA. In addition, recent government proposals have sought to reduce the 12-year reference product exclusivity period. Other aspects of the BPCIA, some of which may impact the BPCIA exclusivity provisions, have also been the subject of recent litigation. As a result, the ultimate impact, implementation, and impact of the BPCIA is subject to significant uncertainty.

As discussed below, the Inflation Reduction Act of 2022 ("IRA") is a significant new law that intends to foster generic and biosimilar competition and to lower drug and biologic costs.

Other U.S. Healthcare Laws and Compliance Requirements

Pharmaceutical companies are subject to additional healthcare regulation and enforcement by the federal government and by authorities in the states and foreign jurisdictions in which they conduct their business. Such laws include, without limitation: the federal Anti-Kickback Statute ("AKS"), the federal False Claims Act ("FCA"), the Health Insurance Portability and Accountability Act ("HIPAA") and similar foreign, federal and state fraud, abuse and transparency laws.

The federal AKS prohibits, among other things, any person or entity from knowingly and willfully offering, paying, soliciting or receiving any remuneration, to induce or in return for either the referral of an individual, or the purchase or recommendation of an item or service for which payment may be made under any federal healthcare program. The term remuneration has been interpreted broadly to include anything of value. The AKS has been interpreted to apply to arrangements between pharmaceutical manufacturers on one hand, and prescribers and purchasers on the other. Our practices may not in all cases meet all of the criteria for protection under a statutory exception or regulatory safe harbor. Failure to meet all of the requirements of a particular applicable statutory exception or regulatory safe harbor does not make the conduct per se illegal under the AKS. Instead, the legality of the arrangement will be evaluated on a case-by-case basis based on a cumulative review of all of its facts and circumstances. 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 false claims laws, including the FCA, which imposes significant penalties and can be enforced by private citizens through civil qui tam actions, and civil monetary penalty laws prohibit any person or entity from, among other things, knowingly presenting, or causing to be presented, a false or fraudulent claim for payment of federal government funds, including federal healthcare programs, such as Medicare and Medicaid. Pharmaceutical and other healthcare companies have been prosecuted under these laws for engaging in a variety of different types of conduct that caused the submission of false claims to federal healthcare programs. Under the AKS, for example, a claim resulting from a violation of the AKS is deemed to be a false or fraudulent claim for purposes of the FCA. The FCA imposes mandatory treble damages and per-violation civil penalties up to approximately $25,000.

HIPAA created additional federal criminal statutes that prohibit, among other things, executing a scheme to defraud any healthcare benefit program, including private third-party payors, and making false statements relating to healthcare matters. A person or entity does not need to have actual knowledge of the healthcare fraud statute implemented under HIPAA or specific intent to violate the statute in order to have committed a violation.

Also, many states have similar, and typically more prohibitive, fraud and abuse statutes or regulations that apply to items and services reimbursed under Medicaid and other state programs, or, in several states, apply regardless of the payor.

The U.S. federal Physician Payments Sunshine Act requires certain manufacturers of drugs and biologics covered by Medicare, Medicaid or the Children's Health Insurance Program, with specific exceptions, to annually report to the Centers for Medicare & Medicaid Services ("CMS") information related to payments or other transfers of value made to various healthcare professionals including physicians, physician assistants, nurse practitioners, and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members.

Ensuring business arrangements with third parties comply with applicable healthcare laws and regulations is a difficult and costly endeavor. If our operations are found to be in violation of any of the federal and state healthcare laws described above or any other current or future governmental regulations that apply to us, we may be subject to significant penalties, including without limitation, civil, criminal and/or administrative penalties, damages, fines, disgorgement, imprisonment, exclusion from participation in government programs, such as Medicare and Medicaid, injunctions, private "qui tam" actions brought by individual whistleblowers in the name of the government, or refusal to allow us to enter into government contracts, contractual damages, reputational harm, administrative burdens, diminished profits and future earnings, additional reporting obligations and oversight if we become subject to a corporate integrity agreement or other agreement to resolve allegations of non-compliance with these laws, and the curtailment or restructuring of our operations, any of which could adversely affect our ability to operate our business and our results of operations.

Data Privacy and Security

Numerous state, federal and foreign laws, govern the collection, dissemination, use, access to, confidentiality and security of personal information, including health-related information. In the United States, numerous federal and state laws and regulations, including state data breach notification laws, state health information privacy laws, and federal and state consumer protection laws and regulations, govern the collection, use, disclosure, and protection of health-related and other personal information could apply to our operations or the operations of our partners. Entities that are found to be in violation of HIPAA or other laws may be subject to significant civil, criminal and administrative fines and penalties and/or additional reporting and oversight obligations. Further, entities that knowingly obtain, use, or disclose certain individually identifiable health information in an improper fashion may be subject to criminal penalties.

Coverage, Pricing and Reimbursement

Significant uncertainty exists as to the coverage and reimbursement status of any product candidates for which we may obtain regulatory approval. In the United States and in foreign markets, sales of any products for which we receive regulatory approval for commercial sale will depend, in part, on the extent to which third-party payors provide coverage and establish adequate reimbursement levels for such products. In the United States, third-party payors include federal and state healthcare programs, private managed care providers, private health insurers and other organizations. Adequate coverage and reimbursement from governmental healthcare programs, such as Medicare and Medicaid in the United States, and commercial payors are critical to new product acceptance.

Third-party payors are increasingly challenging the prices charged for medical products and services, examining the medical necessity and reviewing the cost effectiveness of pharmaceutical or biological products, medical devices and medical services, in addition to questioning 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. Decreases in third-party reimbursement for any product or a decision by a third-party not to cover a product could reduce physician usage and patient demand for the product.

Decisions regarding whether to cover any of our product candidates, if approved, the extent of coverage and amount of reimbursement to be provided are made on a plan-by-plan basis. Further, no uniform policy for coverage and reimbursement exists in the United States, and coverage and reimbursement can differ significantly from payor to payor. Third-party payors often rely upon Medicare coverage policy and payment limitations in setting their own reimbursement rates, but also have their own methods and approval process apart from Medicare determinations. As a result, the coverage determination process is often a time-consuming and costly process that will require us to provide scientific and clinical support for the use of our product candidates to each payor separately, with no assurance that coverage and adequate reimbursement will be applied consistently or obtained in the first instance.

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. In addition, companion diagnostic tests 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.

In addition, the U.S. government, state legislatures and foreign governments have continued implementing cost-containment programs, including price controls, restrictions on coverage and reimbursement and requirements for substitution of generic products. The IRA provides CMS with significant new authorities intended to curb drug costs and to encourage market competition. For the first time, CMS will be able to directly negotiate prescription drug prices and to cap out-of-pocket costs. Each year, CMS will select and negotiate a preset number of high-spend drugs and biologics that are covered under Medicare Part B and Part D that do not have generic or biosimilar competition. These price negotiations will begin in 2023. The IRA also provides a new “inflation rebate” covering Medicare patients that will take effect in 2023 and is intended to counter certain price increases in prescriptions drugs. The inflation rebate provision will require drug manufacturers to pay a rebate to the federal government if the price for a drug or biologic under Medicare Part B and Part D increases faster than the rate of inflation. To support biosimilar competition, beginning in October 2022, qualifying biosimilars whose average sales price (“ASP”) is less than the ASP of its biologic reference product may receive a Medicare Part B payment increase for a period of five years. Separately, if a biologic drug for which no biosimilar exists delays a biosimilar’s market entry beyond two years, CMS will be authorized to subject the biologics manufacturer to price negotiations intended to ensure fair competition. Notwithstanding these provisions, the IRA’s impact on commercialization and competition remains largely uncertain.

Healthcare Reform

In the United States and some foreign jurisdictions, there have been, and continue to be, several legislative and regulatory changes and proposed changes regarding the healthcare system that could prevent or delay marketing approval of product candidates, restrict or regulate post-approval activities, and affect the ability to profitably sell product candidates for which marketing approval is obtained. Among policy makers and payors in the United States and elsewhere, there is significant interest in promoting changes in healthcare systems with the stated goals of containing healthcare costs, improving quality and/or expanding access. In the United States, the pharmaceutical industry has been a particular focus of these efforts and has been significantly affected by major legislative initiatives.

For example, the Affordable Care Act has substantially changed healthcare financing and delivery by both governmental and private insurers. The Affordable Care Act and its implementing regulations, among other things, revised the methodology for calculating rebates for covered outpatient drugs and certain biologics owed by manufacturers to the state and federal government under the Medicaid Drug Rebate Program, increased the minimum Medicaid rebates owed by most manufacturers under the Medicaid Drug Rebate Program, extended the Medicaid Drug Rebate program to utilization of prescriptions of individuals enrolled in Medicaid managed care organizations, subjected manufacturers to new annual fees and taxes for certain branded prescription drugs, and expanded programs designed to test innovative payment models, service delivery models, or value-based arrangements, and fund comparative effectiveness research.

We anticipate that the Affordable Care Act will continue to result in additional downward pressure on coverage and the price that we receive for any approved product, and could seriously harm our business. 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 products. Such reforms could have an adverse effect on anticipated revenue from product candidates that we may successfully develop and for which we may obtain regulatory approval and may affect our overall financial condition and ability to develop product candidates.

In addition, further legislation or regulation could be passed that could harm our business, financial condition and results of operations. Other legislative changes have been proposed and adopted since the Affordable Care Act was enacted.

Notwithstanding the Inflation Reduction Act, continued legislative and enforcement interest exist in the United States with respect to specialty drug pricing practices. Specifically, we expect regulators to continue pushing for transparency to drug pricing, reducing the cost of prescription drugs under Medicare, reviewing the relationship between pricing and manufacturer patient programs, and reforming government program reimbursement methodologies for drugs.

Drug and Biologic Development Process in the European Union

The conduct of clinical trials in the EU is governed by the EU Clinical Trials Regulation (EU) No. 536/2014 ("CTR") which entered into force on January 31, 2022. Under the CTR, a sponsor will be able to submit a single application for approval of a clinical trial through a centralized EU clinical trials portal. One national regulatory authority (the reporting EU member state proposed by the applicant) will take the lead in validating and evaluating the application consult and coordinate with the other concerned member states. If an application is rejected, it may be amended and resubmitted through the EU clinical trials portal. If an approval is issued, the sponsor may start the clinical trial in all concerned member states. However, a concerned EU member state may in limited circumstances declare an "opt-out" from an approval and prevent the clinical trial from being conducted in such member state. The CTR also aims to streamline and simplify the rules on safety reporting, and introduces enhanced transparency requirements such as mandatory submission of a summary of the clinical trial results to the EU Database.

National laws, regulations and the applicable Good Clinical Practice ("GCP") and Good Laboratory Practice standards must also be respected during the conduct of the trials, including the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use ("ICH") guidelines on Good Clinical Practice and the ethical principles that have their origin in the Declaration of Helsinki.

During the development of a medicinal product, the European Medical Agency ("EMA") and national regulators within the EU provide the opportunity for dialogue and guidance on the development program. At the EMA level, this is usually done in the form of scientific advice, which is given by the Committee for Medicinal Products for Human Use ("CHMP") on the recommendation of the Scientific Advice Working Party ("SAWP"). A fee is incurred with each scientific advice procedure, but is significantly reduced for designated orphan medicines. Advice from the EMA is typically provided based on questions concerning, for example, quality (chemistry, manufacturing and controls testing), nonclinical testing and clinical studies, and pharmacovigilance plans and risk-management programs. Advice is not legally binding with regard to any future Marketing Authorization Application ("MAA") of the product concerned.

Drug Marketing Authorization in the European Union

In the EU and in Iceland, Norway and Liechtenstein (together the European Economic Area or "EEA"), after completion of all required clinical testing, pharmaceutical products may only be placed on the market after obtaining a Marketing Authorization ("MA"). To obtain an MA of a drug under European Union regulatory systems, an applicant can submit an MAA through, amongst others, a centralized or decentralized procedure.

The centralized procedure provides for the grant of a single MA by the European Commission ("EC") that is valid for all EU Member States and, after respective national implementing decisions, in the three additional EEA Member States. The centralized procedure is compulsory for specific medicinal products, including for medicines developed by means of certain biotechnological processes, products designated as orphan medicinal products, advanced therapy medicinal products ("ATMP") and medicinal products with a new active substance indicated for the treatment of certain diseases (AIDS, cancer, neurodegenerative disorders, diabetes, auto-immune and viral diseases). For medicinal products containing a new active substance not yet authorized in the EEA before May 20, 2004 and indicated for the treatment of other diseases, medicinal products that constitute significant therapeutic, scientific or technical innovations or for which the grant of a MA through the centralized procedure would be in the interest of public health at EU level, an applicant may voluntarily submit an application for a marketing authorization through the centralized procedure.

Under the centralized procedure, the Committee for Medicinal Products for Human Use ("CHMP"), established at the EMA, is responsible for conducting the initial assessment of a drug. The CHMP is also responsible for several post-authorization and maintenance activities, such as the assessment of modifications or extensions to an existing marketing authorization. Under the centralized procedure, the timeframe for the evaluation of an MAA by the EMA's CHMP is, in principle, 210 days from receipt of a valid MAA. However, this timeline excludes clock stops, when additional written or oral information is to be provided by the applicant in response to questions asked by the CHMP, so the overall process typically takes a year or more, unless the application is eligible for an accelerated assessment. Accelerated assessment might be granted by the CHMP in exceptional cases when a medicinal product is of major interest from the point of view of public health and in particular from the viewpoint of therapeutic innovation. On request, the CHMP can reduce the time frame to 150 days if the applicant provides sufficient justification for an accelerated assessment. The CHMP will provide a positive opinion regarding the application only if it meets certain quality, safety and efficacy requirements. However, the EC has final authority for granting the MA within 67 days after receipt of the CHMP opinion.

The decentralized procedure permits companies to file identical MA applications for a medicinal product to the competent authorities in various EU Member States simultaneously if such medicinal product has not received marketing approval in any EU Member State before. This procedure is available for pharmaceutical products not falling within the mandatory scope of the centralized procedure. The competent authority of a single EU Member State, known as the reference EU Member State, is appointed to review the application and provide an assessment report. Under this procedure, an applicant submits an application based on identical dossiers and related materials, including a draft summary of product characteristics, and draft labeling and package leaflet, to the reference EU Member State and concerned EU Member States. The reference EU Member State prepares a draft assessment report and drafts of the related materials within 120 days after receipt of a valid application. Subsequently each concerned EU Member State must decide whether to approve the assessment report and related materials. If an EU Member State cannot approve the assessment report and related materials on the grounds of potential serious risk to public health, the disputed points are subject to a dispute resolution mechanism and may eventually be referred to the EC, whose decision is binding for all EU Member States.

All new MAAs must include a Risk Management Plan ("RMP"), describing the risk management system that the company will put in place and documenting measures to prevent or minimize the risks associated with the product. The regulatory authorities may also impose specific obligations as a condition of the MA. RMPs and Periodic Safety Update Reports ("PSURs") are routinely available to third parties requesting access, subject to limited redactions.

Marketing Authorizations have an initial duration of five years. After these five years, the authorization may subsequently be renewed on the basis of a reevaluation of the risk-benefit balance. Once renewed, the MA is valid for an unlimited period unless the EC or the national competent authority decides, on justified grounds relating to pharmacovigilance, to proceed with only one additional five-year renewal. Applications for renewal must be made to the EMA at least nine months before the five-year period expires.

Data and Market Exclusivity in the European Union

As in the United States, it may be possible to obtain a period of market and/or data exclusivity in the EU that would have the effect of postponing the entry into the marketplace of a competitor's generic, hybrid or biosimilar product (even if the pharmaceutical product has already received a MA) and prohibiting another applicant from relying on the MA holder's pharmacological, toxicological and clinical data in support of another MA for the purposes of submitting an application, obtaining MA or placing the product on the market. New Chemical Entities ("NCE") approved in the EU qualify for eight years of data exclusivity and 10 years of marketing exclusivity.

An additional non-cumulative one-year period of marketing exclusivity is possible if during the data exclusivity period (the first eight years of the 10-year marketing exclusivity period), the MA holder obtains an authorization for one or more new therapeutic indications that are deemed to bring a significant clinical benefit compared to existing therapies.

The data exclusivity period begins on the date of the product's first MA in the EU. After eight years, a generic product application may be submitted and generic companies may rely on the MA holder's data. However, a generic product cannot launch until two years later (or a total of 10 years after the first MA in the EU of the innovator product), or three years later (or a total of 11 years after the first MA in the EU of the innovator product) if the MA holder obtains MA for a new indication with significant clinical benefit within the eight-year data exclusivity period. Additionally, another noncumulative one-year period of data exclusivity can be added to the eight years of data exclusivity where an application is made for a new indication for a well-established substance, provided that significant pre-clinical or clinical studies were carried out in relation to the new indication. Another year of data exclusivity may be added to the eight years, where a change of classification of a pharmaceutical product has been authorized on the basis of significant pre-trial tests or clinical trials (when examining an application by another applicant for or holder of market authorization for a change of classification of the same substance the competent authority will not refer to the results of those tests or trials for one year after the initial chance was authorized).

Products may not be granted data exclusivity since there is no guarantee that a product will be considered by the European Union's regulatory authorities to include a NCE. Even if a compound is considered to be a NCE and the MA applicant is able to gain the prescribed period of data exclusivity, another company nevertheless could also market another version of the medicinal product if such company can complete a full MAA with their own complete database of pharmaceutical tests, preclinical studies and clinical trials and obtain MA of its product.

European Data Laws

The collection and use of personal health data and other personal data in the EU is governed by the provisions of the European General Data Protection Regulation (EU) 2016/679 ("GDPR") and related data protection laws in individual EU Member States.

The GDPR imposes a number of strict obligations and restrictions on the ability to process (processing includes collecting, analyzing and transferring) personal data of individuals, in particular with respect to health data from clinical trials and adverse event reporting. The GDPR includes requirements relating to the legal basis of the processing (such as consent of the individuals to whom the personal data relates), the information provided to the individuals prior to processing their personal data, the notification obligations to the national data protection authorities, and the security and confidentiality of the personal data. EU Member States may also impose additional requirements in relation to health, genetic and biometric data through their national legislation.

In addition, the GDPR imposes specific restrictions on the transfer of personal data to countries outside of the EU/EEA that are not considered by the EC to provide an adequate level of data protection (including the United States). Appropriate safeguards are required to enable such transfers.

Failure to comply with the requirements of the GDPR and the related national data protection laws of the EU Member States may result in significant monetary fines for noncompliance of up to €20 million or 4% of the annual global revenues of the noncompliant company, whichever is greater, other administrative penalties and a number of criminal offenses (punishable by uncapped fines) for organizations and, in certain cases, their directors and officers, as well as civil liability claims from individuals whose personal data was processed. Data protection authorities from

the different EU Member States may still implement certain variations, enforce the GDPR and national data protection laws differently, and introduce additional national regulations and guidelines, which adds to the complexity of processing personal data in the EU. Guidance developed at both the EU level and at the national level in individual EU Member States concerning implementation and compliance practices are often updated or otherwise revised.

Furthermore, there is a growing trend towards the required public disclosure of clinical trial data in the EU, which adds to the complexity of obligations relating to processing health data from clinical trials. Such public disclosure obligations are provided in the new EU CTR, EMA disclosure initiatives and voluntary commitments by industry. Failing to comply with these obligations could lead to government enforcement actions and significant penalties against us, harm to our reputation, and adversely impact our business and operating results. The uncertainty regarding the interplay between different regulatory frameworks, such as the CTR and the GDPR, further adds to the complexity that we face with regard to data protection regulation.

Additional Regulation

In addition to the foregoing, local, state and federal laws, including in the United States and Israel, regarding such matters as safe working conditions, manufacturing practices, environmental protection, fire hazard control and hazardous substances, including the Occupational Safety and Health Act, the Resource Conservancy and Recovery Act and the Toxic Substances Control Act, affect our business. These and other laws govern our use, handling and disposal of various biological, chemical and radioactive substances used in, and wastes generated by, our operations. If our operations result in contamination of the environment or expose individuals to hazardous or biohazardous substances, we could be liable for damages, environmental remediation, and/or governmental fines. We believe that we are in material compliance with applicable environmental laws and occupational health and safety laws that continued compliance therewith will not have a material adverse effect on our business. We cannot predict, however, how changes in these laws may affect our future operations. We may incur significant costs to comply with such laws and regulations now or in the future.

Competition

The biopharmaceutical industry is intensely competitive and subject to rapid innovation and significant technological advancements. We believe the key competitive factors that will affect the development and commercial success of pegozafermin and any future product candidates are efficacy, safety and tolerability profile, reliability, convenience of dosing, price, the level of generic competition and reimbursement. Our competitors include multinational pharmaceutical companies, specialized biotechnology companies, universities and other research institutions. A number of biotechnology and pharmaceutical companies are pursuing the development or marketing of pharmaceuticals that target the same diseases that we are targeting. Smaller or earlier-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large, established companies. Given the high incidence of NASH, it is likely that the number of companies seeking to develop products and therapies for the treatment of liver and cardio-metabolic diseases, such as NASH, will increase.

If pegozafermin is approved for the treatment of NASH, future competition could also arise from select products currently in development, including: Firsocostat/GS-0976, an ACC inhibitor, and Cilofexor/GS-9674, an FXR agonist, from Gilead Sciences, Inc.; Ervogastat/PF-06865571, a DGAT2 inhibitor, and Clesacostat/PF-05221304, an ACC inhibitor from Pfizer Inc.; Ocaliva, an FXR agonist from Intercept Pharmaceuticals, Inc.; Resmetirom, a beta-thyroid hormone receptor agonist from Madrigal Pharmaceuticals, Inc.; VK2809, a beta-thyroid hormone receptor agonist from Viking Therapeutics, Inc.; Aldafermin, an FGF19 analog from NGM Biopharmaceuticals, Inc.; Efruxifermin, a FGF21 analog from Akero Therapeutics, Inc.; Belapectin, a Galectin-3 inhibitor from Galectin Therapeutics Inc.; Semaglutide, a GLP-1 receptor agonist from Novo Nordisk A/S; Pemvidutide/ALT-801, a dual GLP-1/glucagon agonist from Altimmune; Tirzepatide, a dual GIP/GLP-1 receptor agonist from Eli Lilly and Company; Lanifibranor, a PPAR alpha/delta/gamma agonist from Inventiva; NNC0194-0499, an FGF21 analog from Novo Nordisk; and BOS-580, an FGF21 analog from Boston Pharmaceuticals.

If pegozafermin is approved for the treatment of SHTG, we would face competition from currently approved and marketed products, including statins, fibrates, Vascepa (Pure EPA), and Lovaza (EPA and DHA), as well as generic products. Further competition could arise from products currently in development, including: Olezarsen/AKCEA-APOCIII-LRx, an APOC3 inhibitor from Ionis; Evinacumab, an Anti-ANGPTL3 from Regeneron Pharmaceuticals, Inc.; and ARO-APOC3, an ApoC-III inhibitor from Arrowhead Pharmaceuticals, Inc.

Many of our competitors have substantially greater financial, technical, human and other resources than we do and may be better equipped to develop, manufacture and market technologically superior products. In addition, many of these competitors have significantly longer operating histories and greater experience than we have in undertaking nonclinical studies and human clinical trials of new pharmaceutical products and in obtaining regulatory approvals of human therapeutic products. Many of our competitors have established distribution channels for the commercialization of their products, whereas we have no such channel or capabilities. In addition, many competitors have greater name recognition and more extensive collaborative relationships. As a result, our competitors may obtain regulatory approval of their products more rapidly than we do or may obtain patent protection or other intellectual property rights that limit our ability to develop or commercialize our product candidate or any future product candidates. Our competitors may also develop and succeed in obtaining approval for drugs that are more effective, more convenient, more widely used and less costly or have a better safety profile than our products and these competitors may also be more successful than we are in manufacturing and marketing their products. If we are unable to compete effectively against these companies, then we may not be able to commercialize our product candidate or any future product candidates or achieve a competitive position in the market. This would adversely affect our ability to generate revenue. Our competitors also compete with us in recruiting and retaining qualified scientific, management and commercial personnel, establishing clinical trial sites and enrolling patients for clinical trials, as well as in acquiring technologies complementary to, or necessary for, our programs.

Manufacturing and Supply

We do not own or operate manufacturing facilities for the production of pegozafermin, nor do we have plans to develop our own manufacturing operations in the foreseeable future. We currently rely, and expect to continue to rely, on third parties for the manufacturing of our product candidates for preclinical and clinical testing, as well as for commercial manufacturing if pegozafermin or any future product candidate receives marketing approval.

Pegozafermin drug substance is manufactured by fermentation of a recombinant strain of the bacterium E. coli. Product accumulates as insoluble particles (inclusion bodies) within the cells and is recovered by cell disruption, followed by solubilization of the inclusion bodies, protein refolding and purification with two chromatographic separation columns. Purified material is glycoPEGylated in a 2-step enzymatic reaction where a 20kDa linear glycoPEG moiety is attached to the protein through GalNAc and Sialic Acid linkers.

GlycoPEGylated protein is purified with two chromatographic columns to yield product with target quality attributes. Purified glycoPEGylated protein is concentrated and then formulated to a target concentration with formulation buffer as drug product.

Northway Biotechpharma (“BTPH”) is currently our sole source supplier for pegozafermin. Any reduction or halt in supply of drug substance from BTPH could limit our ability to develop pegozafermin until a replacement contract manufacturer is found and qualified. We are working with BTPH and a second CMO currently based in China (with plans to expand into the United States) on process optimization to support large-scale production for future trials and commercialization.

We have successfully developed a new refrigerated liquid formulation. This formulation is approved by the FDA and is currently in use in our trials. We are currently developing an additional liquid formulation at various concentrations in Pre-Filled Syringe (“PFS”). In addition, we have entered into a contract with a commercial fill vendor.

BTPH Agreement

In May 2018, we entered into a master services agreement with BTPH, under which BTPH agreed to provide us certain services, including development, manufacturing, and storing of pegozafermin, under statements of work for such services to be agreed by the parties from time to time.

Sales and Marketing

We currently have no marketing, sales or distribution capabilities. In order to commercialize any products that are approved for commercial sale, we must either develop a sales and marketing infrastructure or collaborate with third parties that have sales and marketing experience.

We may elect to establish our own sales force to market and sell a product for which we obtain regulatory approval if we expect that the geographic market for a product we develop on our own is limited or that the prescriptions for the product will be written principally by a relatively small number of physicians. If we decide to market and sell any products ourselves, we do not expect to establish direct sales capability until shortly before the products are approved for commercial sale.

We plan to seek third-party support from established pharmaceutical and biotechnology companies for those products that would benefit from the promotional support of a large sales and marketing force. In these cases, we might seek to promote our products in collaboration with marketing partners or rely on relationships with one or more companies with large established sales forces and distribution systems.

Intellectual Property

Our success depends in part upon our ability to protect our core technology and intellectual property. To protect our intellectual property rights, we rely on patents, trademarks, copyrights and trade secret laws, confidentiality procedures, and employee disclosure and invention assignment agreements. Our intellectual property is critical to our business and we strive to protect it through a variety of approaches, including by obtaining and maintaining patent protection in the United States and internationally for our product candidates, novel biological discoveries, new targets and applications, and other inventions that are important to our business. For our product candidates, we generally intend to pursue patent protection covering compositions of matter, methods of making and methods of use. As we continue the development of our product candidates, we plan to identify additional means of obtaining patent protection that would potentially enhance commercial success, including pursuit of claims directed to new therapeutic indications.

FGF21 Patents

Our FGF21 patent portfolio includes six families:

The first family is entitled “Remodeling and GlycoPEGylation of Fibroblast Growth Factor (FGF)”. This patent family provides granted patent protection in 39 countries around the globe, including the United States (U.S. Patent Number 9,200,049, expiry date: June 25, 2028; and U.S. Patent Number 10,874,714, expiry date: October 10, 2028), Canada, Europe (broadly), and Japan (latter three expire October 31, 2025) for FGF21 conjugates comprising a variety of modifying groups that can be attached at several different amino acid positions. GlycoPEGylated FGF21 is specifically claimed. The granted claims broadly protect our lead drug candidate pegozafermin and pharmaceutical compositions thereof, as well as methods for making and using pegozafermin to treat FGF21 deficiency in a patient in need thereof.

The second family is entitled “Mutant FGF-21 Peptide Conjugate and Uses Thereof” and is specifically directed to pegozafermin. The Patent Cooperation Treaty (“PCT”) Patent Application for this family was filed on September 4, 2018 (PCT/IB2018/00112). A U.S. Prioritized Examination Continuation Patent Application (Application Serial No. 16/225,640) was filed on December 19, 2018 as a continuation of PCT/IB2018/0112 and from which U.S. Patent Number 10,407,479 was issued on September 10, 2019. The term of the U.S. Patent Number 10,407,479 is September 4, 2038. The issued claims are directed to pegozafermin and a defined genus specifically encompassing pegozafermin and compositions thereof (including site-specific mutations at positions 173 and 176), as well as methods for making and using pegozafermin for a variety of therapeutic indications. Such indications include methods for treating NASH or metabolic syndrome. Subjects where there is a need to reduce blood glucose or to reduce HbA1C include those afflicted with diabetes Type 2, NASH and metabolic syndrome. The claims encompass different therapeutic regimens for administering pegozafermin (e.g., once a week or once every two weeks), which regimens are based on pegozafermin’s surprisingly long half-life in vivo. This patent family provides granted patent protection of pegozafermin in 24 ex-United States jurisdictions around the globe: Australia, Canada, China, Europe (broadly), Israel, Japan, Korea and Hong Kong (expiry date: September 4, 2038). One U.S. Patent Application and one China Patent Application are pending in this family.

The third family is entitled “Methods Of Treatment Using Mutant FGF-21 Peptide Conjugates”. This patent family provides granted patent protection in United States (U.S. Patent Number 11,427,623). The term of the U.S. Patent Number 11,427,623 is September 4, 2038. One U.S. Patent Application is pending in this family.

The fourth family is entitled “Methods for promoting weight loss”. A PCT application was filed January 29, 2021 (PCT/IB2021/000044) with claims directed towards method to reduce total body weight, body fat content and/or BMI. A United States National phase application was filed July 20, 2022. This patent application has not yet been published.

The fifth family is entitled “Liquid Formulations Comprising Mutant FGF-21 Peptide Pegylated Conjugates” with claims directed to on stable liquid formulation of FGF21. A PCT Patent Application for this family was filed on March 10, 2022. A U.S. Prioritized Examination Patent Application was filed on March 10, 2022. We will continue to file patent applications to cover various formulations of FGF21.

The sixth family is entitled “Chemical Synthesis of Cytidine-5'-Monophospho-N-Glycyl-Sialic Acid” with claims directed to the chemical synthesis of Cytidine-5'-Monophospho-N-Glycyl-Sialic Acid. A PCT Patent Application for this family was filed on December 20, 2022.

We expect to continue to file patent applications to cover method of treating different indications.

FASN Patents

Our FASN patent portfolio currently consists of three patent families, including patents and/or patent applications in the United States, the European Patent Convention, Canada, Mexico, Israel, China and Japan.

The first patent family, directed to TEV-48317, which we acquired from Teva under the FASN Agreement, and other 1,4-substituted piperidine-based FASN inhibitors, is currently protected by three granted U.S. patents that cover these compounds, pharmaceutical compositions comprising these compounds, and/or methods of treating FASN-mediated disorders using these compounds. The non-extended term for these patents would expire on June 17, 2036. A pending U.S. application has also been filed. The first patent family also includes twelve foreign patents and two foreign patent applications. The second patent family is directed to other 1,4-substituted piperidine-based FASN inhibitors, pharmaceutical compositions, and methods of treating FASN-mediated disorders. The second patent family includes one granted U.S. patent, one U.S. patent application, nine foreign patents, and two foreign patent applications. The third patent family is directed to spiropiperidine FASN inhibitors, pharmaceutical compositions containing these compounds, and methods of treating FASN-mediated disorders using these compounds. The third patent family includes one granted U.S. patent, one U.S. patent application and five foreign patent applications.

Employees

As of December 31, 2022, we had 45 full-time employees, of which 33 employees are engaged in research and development activities. 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.

Corporate Information

We were incorporated in January 2018 in Israel under the name 89Bio Ltd. 89bio, Inc., the registrant whose name appears on the cover page of this Annual Report on Form 10-K, was incorporated in June 2019 for the purpose of an internal reorganization transaction. In September 2019, all of the equity holders of 89Bio Ltd. exchanged 100% of the equity of 89Bio Ltd. for 100% of the equity of 89bio, Inc. Following this exchange, 89Bio Ltd. became a wholly owned subsidiary of 89bio, Inc.

Our principal executive offices are located at 142 Sansome Street, San Francisco, California 94104 and our telephone number is (415) 432-9270. Our website is *www.89bio.com*. Information contained on or accessible through our website is not a part of this Annual Report on Form 10-K, and the inclusion of our website address in this Annual Report on Form 10-K is an inactive textual reference only.

We file electronically with the SEC our Annual Report on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and amendments to those reports filed or furnished pursuant to Section 13(a) or 15(d) of the Securities Exchange Act of 1934, as amended (the "Exchange Act"). We make available on our website at *www.89bio.com*, under "Investors," free of charge, copies of these reports as soon as reasonably practicable after filing or furnishing these reports with the SEC.

Implications of Being an Emerging Growth Company and a Smaller Reporting Company

We are an "emerging growth company", as defined in Section 2(a) of the Securities Act of 1933, as amended (the "Securities Act"), as modified by the Jumpstart Our Business Startups Act of 2012 (the "JOBS Act"), and we may take advantage of certain exemptions from various reporting requirements that are applicable to other public companies that are not emerging growth companies, including relief from the auditor attestation requirements of Section 404 of the Sarbanes-Oxley Act of 2002, as amended, less extensive disclosure obligations regarding executive compensation in our registration statements, periodic reports and proxy statements, exemptions from the requirements to hold a nonbinding advisory vote on executive compensation, and exemptions from stockholder approval of any golden parachute payments not previously approved. We may also elect to take advantage of other reduced reporting requirements in future filings. As a result, our stockholders may not have access to certain information that they may deem important and the information that we provide to our stockholders may be different than, and not comparable to, information presented by other public reporting companies. We could remain an emerging growth company until the earlier of (1) the last day of the year following the fifth anniversary of the completion of our initial public offering ("IPO"), (2) the last day of the year in which we have total annual gross revenue of at least $1.235 billion, (3) the last day of the year in which we are deemed to be a "large accelerated filer" as defined in Rule 12b-2 under the Exchange Act, which would occur if the market value of our common stock held by non-affiliates exceeded $700.0 million as of the last business day of the second fiscal quarter of such year or (4) the date on which we have issued more than $1.0 billion in non-convertible debt securities during the prior three-year period.

In addition, the JOBS Act also provides that an emerging growth company may take advantage of the extended transition period provided in the Securities Act for complying with new or revised accounting standards. An emerging growth company may therefore delay the adoption of certain accounting standards until those standards would otherwise apply to private companies. We have elected to avail ourselves of this exemption and, as a result, will not be subject to the same implementation timing for new or revised accounting standards as are required of other public companies that are not emerging growth companies, which may make comparison of our consolidated financial information to those of other public companies more difficult.

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 (i) 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 (ii) 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.

Item 1A. Risk Factors.

An investment in our common stock involves a high degree of risk. You should carefully consider the risks and uncertainties described below before deciding whether to make an investment decision with respect to shares of our common stock. You should also refer to the other information contained in this Annual Report on Form 10-K, including "Management's Discussion and Analysis of Financial Condition and Results of Operations" and our audited consolidated financial statements and related notes. Our business, financial condition, results of operations and prospects could be materially and adversely affected by any of these risks or uncertainties. In any such case, the trading price of our common stock could decline, and you could lose all or part of your investment. We caution you that the risks, uncertainties and other factors referred to below and elsewhere in this Annual Report on Form 10-K may not contain all of the risks, uncertainties and other factors that may affect our future results and operations. Moreover, new risks will emerge from time to time. It is not possible for our management to predict all risks.

Risk Factor Summary

Investing in our common stock involves significant risks. You should carefully consider the risks described below before making a decision to invest in our common stock. If we are unable to successfully address these risks and challenges, our business, financial condition, results of operations, or prospects could be materially adversely affected. In such case, the trading price of our common stock would likely decline, and you may lose all or part of your investment. Below is a summary of some of the risks we face.

- We are a clinical-stage biopharmaceutical company with a limited operating history and no products approved for commercial sale. We have incurred net losses since our inception, we expect to incur significant and increasing operating losses and we may never be profitable. Our stock is a highly speculative investment.
- Our business depends on the success of pegozafermin, our only product candidate under clinical development, which has not completed a pivotal trial. If we are unable to obtain regulatory approval for and successfully commercialize pegozafermin or other future product candidates, or we experience significant delays in doing so, our business will be materially harmed.
- We will require substantial additional capital to finance our operations, which may not be available to us on acceptable terms, or at all. As a result, we may not complete the development and commercialization of pegozafermin or develop new product candidates.
- Clinical drug development involves a lengthy and expensive process with uncertain timelines and uncertain outcomes, and the results of prior preclinical or clinical trials are not necessarily predictive of our future results.
- The ongoing COVID-19 pandemic has resulted and may in the future result in significant disruptions to our clinical trials or other business operations, which could have a material adverse effect on our business.
- If we experience delays in clinical testing, our commercial prospects will be adversely affected, our costs may increase and our business may be harmed.
- If we encounter difficulties in enrolling patients in our clinical trials, our clinical development activities could be delayed or otherwise adversely affected.
- We have relied on, and expect to continue to rely on, third-party manufacturers and vendors to produce and release pegozafermin or any future product candidates. Any failure by a third-party to produce and release acceptable product candidates for us pursuant to our specifications and regulatory standards may delay or impair our ability to initiate or complete our clinical trials, obtain and maintain regulatory approvals or commercialize approved products.
- Pegozafermin and any future product candidates may cause undesirable side effects or have other properties that could delay or prevent their regulatory approval or limit the commercial profile of an approved label.

- We are developing pegozafermin for the treatment of NASH, an indication for which there are no approved products, and the treatment of SHTG. The requirements for approval of pegozafermin by the FDA and comparable foreign regulatory authorities may be difficult to predict and may change over time, which makes it difficult to predict the timing and costs of the clinical development.
- Lack of efficacy, adverse events or undesirable side effects may emerge in clinical trials conducted by third parties developing FGF product candidates, which could adversely affect our stock price, our ability to attract additional capital and our development program.
- Interim, topline and preliminary data from our clinical trials that we announce or publish from time to time may change as more patient data become available and are subject to audit and verification procedures that could result in material changes in the final data.
- The manufacture of biologic products is complex and we are subject to many manufacturing risks, any of which could substantially increase our costs and limit supply of our products.
- We face substantial competition, which may result in others discovering, developing or commercializing competing products before or more successfully than us.
- Unstable market and economic conditions may have serious adverse consequences on our business and financial condition.
- Our Loan and Security Agreement contains certain covenants that could adversely affect our operations and, if an event of default were to occur, we could be forced to repay any outstanding indebtedness sooner than planned and possibly at a time when we do not have sufficient capital to meet this obligation.
- Pegozafermin has not received regulatory approval. If we are unable to obtain regulatory approvals to market pegozafermin or any future product candidates, our business will be adversely affected.
- Our success depends upon our ability to obtain and maintain intellectual property protection for our products and technologies.
- We rely on a license from Teva and a sublicense from ratiopharm to patents and know-how related to glycoPEGylation technology that are used in the development, manufacture and commercialization of pegozafermin. Any termination or loss of significant rights, including the right to glycoPEGylation technology, or breach, under these agreements or any future license agreement related to our product candidates, would materially and adversely affect our ability to continue the development and commercialization of the related product candidates.

Risks Related to Our Business and Industry

We are a clinical-stage biopharmaceutical company with a limited operating history and no products approved for commercial sale. We have incurred net losses since our inception, we expect to incur significant and increasing operating losses and we may never be profitable. Our stock is a highly speculative investment.

We are a clinical-stage biopharmaceutical company with a limited operating history that may make it difficult to evaluate the success of our business to date and to assess our future viability. We commenced operations in 2018, and to date, our operations have been focused on organizing and staffing our company, raising capital, acquiring our initial product candidate, pegozafermin, licensing certain related technology, conducting research and development activities, including preclinical studies and clinical trials, and providing general and administrative support for these operations. Investment in biopharmaceutical product development is highly speculative because it entails substantial upfront capital expenditures and significant risk that any potential product candidate will fail to demonstrate adequate effect and/or an acceptable safety profile, gain regulatory approval and become commercially viable. We have no products approved for commercial sale, we have not generated any revenue from product sales to date and we continue to incur significant research and development and other expenses related to our ongoing operations. We have limited experience as a company conducting clinical trials and no experience as a company commercializing any products.

Pegozafermin is in development and, to date, we have not generated any revenue from the licensing or commercialization of pegozafermin. We will not be able to generate product revenue unless and until pegozafermin or any future product candidate, alone or with future partners, successfully completes clinical trials, receives regulatory approval and is successfully commercialized. As pegozafermin is in development, we do not expect to receive revenue from it for a number of years, if ever. Although we may seek to obtain revenue from collaboration or licensing agreements with third parties, we currently have no such agreements that could provide us with material, ongoing future revenue and we may never enter into any such agreements.

We are not profitable and have incurred net losses since our inception. Consequently, predictions about our future success or viability may not be as accurate as they would be if we had a longer operating history or a history of successfully developing and commercializing pharmaceutical products. We have spent, and expect to continue to spend, significant resources to fund research and development of, and seek regulatory approvals for, pegozafermin and any future product candidates. We expect to incur substantial and increasing operating losses over the next several years as our research and development, clinical trials and manufacturing activities increase. In addition, because of the numerous risks and uncertainties associated with pharmaceutical product development, including that our product candidates may not advance or may take longer than expected to advance through development or may not achieve the endpoints of applicable clinical trials, we are unable to predict the timing or amount of increased expenses, or if or when we will achieve or maintain profitability. The size of our future net losses will depend, in part, on the rate of future growth of our expenses and our ability to generate revenue. The net losses we incur may fluctuate significantly from quarter-to-quarter such that a period-to-period comparison of our results of operations may not be a good indication of our future performance. Even if we eventually generate product revenue, we may never be profitable and, if we do achieve profitability, we may not be able to sustain or increase profitability on a quarterly or annual basis.

Our business depends on the success of pegozafermin, our only product candidate under clinical development, which has not completed a pivotal trial. If we are unable to obtain regulatory approval for and successfully commercialize pegozafermin or other future product candidates, or we experience significant delays in doing so, our business will be materially harmed.

The primary focus of our product development is pegozafermin for the treatment of patients with NASH and the treatment of patients with SHTG. Currently, pegozafermin is our only product candidate under clinical development. This may make an investment in our company riskier than similar companies that have multiple product candidates in active development and that therefore may be able to better sustain a failure of a lead candidate. Successful continued development and ultimate regulatory approval of pegozafermin for the treatment of NASH or SHTG is critical to the future success of our business. We have invested, and will continue to invest, a significant portion of our time and financial resources in the clinical development of pegozafermin. If we cannot successfully develop, obtain regulatory approval for and commercialize pegozafermin, we may not be able to continue our operations. The future regulatory and commercial success of pegozafermin is subject to a number of risks, including that if approved for NASH or SHTG, pegozafermin will likely compete with products that may reach approval for the treatment of NASH prior to pegozafermin, products that are currently approved for the treatment of SHTG and the off-label use of currently marketed products for NASH and SHTG.

We will require substantial additional capital to finance our operations, which may not be available to us on acceptable terms, or at all. As a result, we may not complete the development and commercialization of pegozafermin or develop new product candidates.

As a clinical-stage biopharmaceutical company, our operations have consumed significant amounts of cash since our inception. We expect our research and development expenses to increase in connection with our ongoing activities, particularly as we conduct clinical trials of and seek regulatory approvals for pegozafermin. We believe that our existing cash and cash equivalents and short-term available-for-sale securities will fund our projected operating requirements for a period of at least one year from the date this Annual Report on Form 10-K is filed with the SEC.

We will require additional capital to discover, develop, obtain regulatory approval for and commercialize pegozafermin and any future product candidates. Our ability to complete new and ongoing clinical trials for pegozafermin may be subject to our ability to raise additional capital. We do not have any committed external source of funds other than as a result of any sales that we may make pursuant to the Sales Agreement for our ATM Facility (defined below) and proceeds from our 2023 Loan Agreement, which are subject to the achievement of certain milestones and/or consent of the lenders. We expect to finance future cash needs through public or private equity or debt offerings or product collaborations. Additional capital may not be available in sufficient amounts or on reasonable terms, if at all. The current market environment for small biotechnology companies, like 89bio, and broader macroeconomic factors may preclude us from successfully raising additional capital.

If we do not raise additional capital, we may not be able to expand our operations or otherwise capitalize on our business opportunities, our business and financial condition will be negatively impacted and we may need to: significantly delay, scale back or discontinue research and discovery efforts and the development or commercialization of any product candidates or cease operations altogether; seek strategic alliances for research and development programs when we otherwise would not, or at an earlier stage than we would otherwise desire or on terms less favorable than might otherwise be available; or relinquish, or license on unfavorable terms, our rights to technologies or any product candidates that we otherwise would seek to develop or commercialize ourselves.

In addition, if pegozafermin receives approval and is commercialized, we will be required to make milestone and royalty payments to Teva Pharmaceutical Industries Ltd ("Teva"), from whom we acquired certain patents and intellectual property rights relating to pegozafermin, and from whom we licensed patents and know-how related to glycoPEGylation technology that is used in the manufacture of pegozafermin. For additional information regarding this license agreement, please see Note 5 of our accompanying audited consolidated financial statements.

Clinical drug development involves a lengthy and expensive process with uncertain timelines and uncertain outcomes, and the results of prior preclinical or clinical trials are not necessarily predictive of our future results.

Pegozafermin and any future product candidates will be subject to rigorous and extensive clinical trials and extensive regulatory approval processes implemented by the FDA and comparable foreign regulatory authorities before obtaining marketing approval from these regulatory authorities. The drug development and approval process is lengthy and expensive, and approval is never certain. Investigational new drugs, such as pegozafermin, may not prove to be safe and effective in clinical trials. We have no direct experience as a company in conducting pivotal trials required to obtain regulatory approval. We may be unable to conduct clinical trials at preferred sites, enlist clinical investigators, enroll sufficient numbers of participants or begin or successfully complete clinical trials in a timely fashion, if at all. In addition, the design of a clinical trial can determine whether its results will support approval of a product, and flaws in the design of a clinical trial may not become apparent until the clinical trial is well advanced. We may be unable to design and execute a clinical trial to support regulatory approval. Even if a current clinical trial is successful, it may be insufficient to demonstrate that pegozafermin is safe or effective for registration purposes.

There is a high failure rate for drugs and biologic products proceeding through clinical trials. Failure can occur at any time during the clinical trial process. The results of preclinical studies and early clinical trials of pegozafermin or any future product candidate may not be predictive of the results of later-stage clinical studies or trials and the results of studies or trials in one set of patients or line of treatment may not be predictive of those obtained in another. In fact, many companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in late-stage clinical trials even after achieving promising results in preclinical studies and earlier stage clinical trials. In addition, data obtained from preclinical and clinical activities is subject to varying interpretations, which may delay, limit or prevent regulatory approval. It is impossible to predict when or if pegozafermin or any future product candidate will prove effective or safe in humans or will receive regulatory approval. Owing in part to the complexity of biological pathways, pegozafermin or any future product candidate may not demonstrate in patients the biochemical and pharmacological properties we anticipate based on laboratory studies or earlier stage clinical trials, and they may interact with human biological systems or other drugs in unforeseen, ineffective or harmful ways. The number of patients exposed to product candidates and the average exposure time in the clinical development programs may be inadequate to detect rare adverse events or findings that may only be detected once a product candidate is administered to more patients and for greater periods of time. To date, our Phase 1a, Phase 1b/2a and Phase 2 clinical trials have involved small patient populations and, because of the small sample size in

such trials, the results of these clinical trials may be subject to substantial variability, including the inherent variability associated with biopsies in NASH patients, and may not be indicative of either future interim results or final results in future trials of patients with liver or cardio-metabolic diseases. If we are unable to successfully demonstrate the safety and efficacy of pegozafermin or other future product candidates and receive the necessary regulatory approvals, our business will be materially harmed.

The ongoing COVID-19 pandemic has resulted and may in the future result in significant disruptions to our clinical trials or other business operations, which could have a material adverse effect on our business.

Our business and its operations, including but not limited to our research and development activities, have been adversely affected by health epidemics in regions where we have business operations, and such health epidemics have caused and could continue to cause significant disruption in the operations of third parties upon whom we rely. In response to COVID-19, we have implemented hybrid work policy. The effects of which may negatively impact our growth, including our ability to recruit and onboard new employees, and productivity.

The COVID-19 pandemic has impacted execution and enrollment of our trials. Given the surges in cases of COVID-19 experienced previously and uncertainty regarding other variants, we cannot predict how our ongoing or future trials may be impacted.

In addition, COVID-19 has impacted and may continue to impact personnel at third-party manufacturing facilities in the United States, Europe and other countries, or the availability or cost of materials we use or require to conduct our business, including product development, which would disrupt our supply chain.

The COVID-19 pandemic continues to evolve. The ultimate impact of the COVID-19 pandemic or a similar public health emergency is highly uncertain and subject to change. We do not yet know the full extent of potential delays or impacts on our business, our clinical trials, healthcare systems or the global economy as a whole. However, any one or a combination of these events could have an adverse effect on the operation of and results from our clinical trials and on our other business operations, including preventing or delaying approval for pegozafermin.

If we experience delays in clinical testing, our commercial prospects will be adversely affected, our costs may increase and our business may be harmed.

We cannot guarantee that we will be able to initiate and complete clinical trials and successfully accomplish all required regulatory activities or other activities necessary to gain approval and commercialize pegozafermin or any future product candidates. We currently have two active investigational new drug ("IND") applications with the FDA in the United States for pegozafermin. In the future, we may file an additional IND with another division for any future indications or future product candidates. If any such future IND is not approved by the FDA, our clinical development timeline may be negatively impacted and any future clinical programs may be delayed or terminated. As a result, we may be unable to obtain regulatory approvals or successfully commercialize our products. We do not know whether any other clinical trials will begin as planned, will need to be restructured or will be completed on schedule, or at all. Our product development costs will increase if we experience delays in clinical testing. Significant clinical trial delays also could shorten any periods during which we may have the exclusive right to commercialize pegozafermin and any future product candidates or allow our competitors to bring products to market before we do, which would impair our ability to successfully commercialize pegozafermin or any future product candidates and may harm our business, results of operations and prospects. Our or our future collaborators' inability to timely complete clinical development could result in additional costs to us as well as impair our ability to generate product revenue, continue development, commercialize pegozafermin and any future product candidates, reach sales milestone payments and receive royalties on product sales. In addition, if we make changes to a product candidate including, for example, a new formulation, we may need to conduct additional nonclinical studies or clinical trials to bridge or demonstrate the comparability of our modified product candidate to earlier versions, which could delay our clinical development plan or marketing approval for our current product candidate and any future product candidates.

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

The timely completion of clinical trials largely depends on patient enrollment. We may encounter delays in enrolling, or be unable to enroll, a sufficient number of patients to complete any of our future clinical trials, and even once enrolled, we may be unable to retain a sufficient number of patients to complete any of our trials. Furthermore, there are inherent difficulties in diagnosing NASH, which can currently only be definitively diagnosed through a liver biopsy, and identifying SHTG patients. Specifically, identifying patients most likely to meet NASH enrollment criteria on biopsy is an on-going challenge, with existing clinical indicators lacking both sensitivity and specificity. As a result, NASH trials often suffer from high levels of screen failure following central review of the baseline liver biopsy, which can lead to lower enrollment. As a result of such difficulties and the significant competition for recruiting NASH and SHTG patients in clinical trials, we or our future collaborators may be unable to enroll the patients we need to complete clinical trials on a timely basis, or at all. We plan to leverage the safety database from the SHTG Phase 3 program across both the SHTG and NASH indications. If we are not able enroll enough patients in our trials sufficient to support the safety database, our ability to advance the development of pegozafermin may be adversely affected.

In addition, our competitors, some of whom have significantly greater resources than we do, are conducting clinical trials for the same indications and seek to enroll patients in their studies that may otherwise be eligible for our clinical studies or trials. Since the number of qualified clinical investigators is limited, we expect to conduct some of our clinical trials at the same clinical trial sites that some of our competitors use, which could further reduce the number of patients who are available for our clinical trials in these sites. Our inability to enroll a sufficient number of patients for our clinical trials would result in significant delays or may require us to abandon one or more clinical trials altogether. Even if we are able to enroll a sufficient number of patients in our clinical studies or trials, delays in patient enrollment may result in increased costs or may affect the timing or outcome of our clinical trials, which could prevent completion of these trials and adversely affect our ability to advance the development of pegozafermin and any future product candidates.

We have relied on, and expect to continue to rely on, third-party manufacturers and vendors to produce and release pegozafermin or any future product candidates. Any failure by a third-party to produce and release acceptable product candidates for us pursuant to our specifications and regulatory standards may delay or impair our ability to initiate or complete our clinical trials, obtain and maintain regulatory approvals or commercialize approved products.

We do not own or operate manufacturing facilities for the production of clinical or commercial quantities of our product candidates, and we lack the resources and the capabilities to do so. As a result, we currently rely, and expect to rely for the foreseeable future, on third-party manufacturers to supply us with pegozafermin and any future product candidates. We currently have a sole source relationship with BTPH pursuant to which they supply us with pegozafermin. If there should be any disruption in our supply arrangement with BTPH, including any adverse events affecting BTPH, it could have a negative effect on the clinical development of pegozafermin and other operations while we work to identify and qualify an alternate supply source. In addition, we will require large quantities of pegozafermin for large clinical trials and to commercialize pegozafermin. Our current manufacturer may not be able to scale production to the larger quantities. We have identified a manufacturing partner for commercial-scale manufacturing, however, we cannot guarantee that such partner will be able to scale up and produce the quantities we would require to commercialize pegozafermin.

We do not have a long-term supply agreement with any third-party manufacturer. Reliance on third-party manufacturers entails risks to which we would not be subject if we manufacture product candidates or products ourselves. For example, if we do not maintain our key manufacturing relationships, we may fail to find replacement manufacturers or develop our own manufacturing capabilities in a timely manner or at all, which could delay or impair our ability to obtain regulatory approval for our products and substantially increase our costs or deplete profit margins, if any. If we do find replacement manufacturers, we may not be able to enter into agreements with them on terms and conditions favorable to us, and there could be a substantial delay before new facilities could be qualified and registered with the FDA and other comparable foreign regulatory authorities.

We have begun producing certain of the reagents required for the glycoPEGylation at BTPH using the know-how transferred to us from Teva under our Reagent Supply and Technology Transfer Agreement. We have not completed the manufacturing process for all these reagents and cannot guarantee that we will be able to produce them successfully, or scale up our production for the quantities needed for commercialization.

Teva supplied us with certain reagents until December 31, 2022. We transferred the manufacturing of such reagents to new suppliers prior to the end of 2022. Any significant delay in the acquisition or decrease in the availability of these raw materials from suppliers could considerably delay the manufacture of pegozafermin, which could adversely impact the timing of any planned trials or the regulatory approvals of pegozafermin.

We rely on third-party vendors for our assay development and testing. If such third-party vendors are unable to successfully produce or test such assays, it may substantially increase our cost or could adversely impact the timing of any planned trials or the regulatory approvals of pegozafermin.

The FDA and other comparable foreign regulatory authorities require manufacturers to register manufacturing facilities. The FDA and other comparable foreign regulatory authorities also inspect these facilities to confirm compliance with cGMP. We have little to no control regarding the occurrence of third-party manufacturer incidents. Any failure to comply with cGMP requirements or other FDA or comparable foreign regulatory requirements could adversely affect our clinical research activities and our ability to develop pegozafermin or any future product candidates and market our products following approval. Our sole source supplier, BTPH, has not yet manufactured a commercial product, and as a result, has not been subject to inspection by the FDA and other comparable foreign regulatory authorities.

Our current and anticipated future dependence upon others for the manufacture of our product candidates may adversely affect our future profit margins and our ability to develop our product candidates and commercialize any products that receive regulatory approval on a timely basis. Supply chain issues, including those resulting from the COVID-19 pandemic and the ongoing war in Ukraine, may affect our third-party vendors and cause delays. Furthermore, since we have engaged a manufacturer located in China, we are exposed to the possibility of product supply disruption and increased costs in the event of changes in the policies of the United States or Chinese

governments, political unrest or unstable economic conditions in China. If we are required to change manufacturers for any reason, we will be required to verify that the new manufacturer maintains facilities and procedures that comply with quality standards and with all applicable regulations and guidelines. For example, in the event that we need to switch our third-party manufacturer of pegozafermin from BTPH, which is our sole manufacturing source for pegozafermin, we anticipate that the complexity of the glycoPEGylation manufacturing process may materially impact the amount of time it may take to secure a replacement manufacturer. The delays associated with the verification of a new manufacturer, if we are able to identify an alternative source, could negatively affect our ability to develop product candidates in a timely manner or within budget.

Pegozafermin and any future product candidates may cause undesirable side effects or have other properties that could delay or prevent their regulatory approval or limit the commercial profile of an approved label.

Undesirable side effects caused by pegozafermin or any future product candidates could cause us or regulatory authorities to interrupt, delay or halt clinical trials and could result in a more restrictive label or the delay or denial of regulatory approval by the FDA or other comparable foreign regulatory authorities. Additional clinical studies may be required to evaluate the safety profile of pegozafermin or any future product candidates. As with other drugs, we have seen evidence of adverse effects in animal and human studies and it is possible that other adverse effects will become apparent in ongoing or future animal or human safety studies. It may be difficult to discern whether certain events or symptoms observed during our clinical trials or by patients using our approved products are related to pegozafermin or any future product candidates or approved products or some other factor. As a result, we and our development programs may be negatively affected even if such events or symptoms are ultimately determined to be unlikely related to pegozafermin or any future product candidates or approved products. Further, we expect that pegozafermin will require multiple administrations via subcutaneous injection in the course of a clinical trial. This chronic administration increases the risk that rare adverse events or chance findings are discovered in the commercial setting, where pegozafermin would be administered to more patients or for greater periods of time, that were not uncovered by our clinical drug development programs.

We are developing pegozafermin for the treatment of NASH, an indication for which there are no approved products, and the treatment of SHTG. The requirements for approval of pegozafermin by the FDA and comparable foreign regulatory authorities may be difficult to predict and may change over time, which makes it difficult to predict the timing and costs of the clinical development.

We are developing pegozafermin for the treatment of NASH, an indication for which there are no approved products. Although there are guidelines issued by the FDA for the development of drugs for the treatment of NASH, the development of a novel product candidates such as pegozafermin may be more expensive and take longer than for other, better known or extensively studied product candidates. As other companies are in later stages of clinical trials for their potential NASH therapies, we expect that the path for regulatory approval for NASH therapies may continue to evolve in the near term as these other companies refine their regulatory approval strategies and interact with regulatory authorities. Such evolution may impact our future clinical trial designs, including trial size and endpoints, in ways that we cannot predict today. In particular, regulatory authority expectations about liver biopsy data may evolve especially as more information is published about the inherent variability in liver biopsy data. Certain of our competitors have experienced regulatory setbacks for NASH therapies following communications from the FDA. We currently do not know the impact, if any, that these setbacks could have on the path for regulatory approval for NASH therapies generally or for pegozafermin. Furthermore, the histology endpoints from our Phase 2b ENLIVEN trial may not be accepted as primary endpoints for a pivotal Phase 3 trial or for FDA approval.

We are also developing pegozafermin for the treatment of SHTG. Clinical trials for the treatment of SHTG may be relatively costly and time-consuming. In addition, the requirements for approval by the FDA and comparable foreign regulatory authorities may change over time. If the FDA disagrees with our trial and program design for our planned Phase 3 program for SHTG or requires additional evidence to support a successful submission for approval, we may be required to make changes to our program design that could impact timelines and cost.

Our anticipated development costs would likely increase if development of pegozafermin or any future product candidate is delayed because we are required by the FDA to perform studies or trials in addition to, or different from, those that we currently anticipate, or make changes to ongoing or future clinical trial designs. In addition, if we are unable to leverage our safety database for both SHTG and NASH indications, we may be required to perform additional trials, which would result in increased costs and may affect the timing or outcome of our clinical trials.

Lack of efficacy, adverse events or undesirable side effects may emerge in clinical trials conducted by third parties developing FGF product candidates, which could adversely affect our stock price, our ability to attract additional capital and our development program.

Lack of efficacy, adverse events or undesirable side effects may emerge in clinical trials conducted by third parties developing FGF product candidates like ours. For example, Novo Nordisk, Akero Therapeutics, Inc. and Boston Pharmaceuticals are also developing FGF21 product candidates for the treatment of NASH. We have no control over their clinical trials or development program, and lack of efficacy, adverse events or undesirable side effects experienced by subjects in their clinical trials could adversely affect our stock price, our ability to attract additional capital and our clinical development plans for pegozafermin or even the viability or prospects of pegozafermin as a product candidate, including by creating a negative perception of FGF therapeutics by healthcare providers or patients.

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

From time to time, we may publicly disclose preliminary or topline data from our clinical trials, which 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. 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 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. From time to time, we may also disclose interim data from our clinical trials. 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.

The manufacture of biologic products is complex and we are subject to many manufacturing risks, any of which could substantially increase our costs and limit supply of our products.

To date, pegozafermin has been manufactured by a single third-party manufacturer, BTPH, solely for preclinical studies and clinical trials. The process of manufacturing pegozafermin, and in particular, the glycoPEGylation process, is complex, highly regulated and subject to several risks and requires significant expertise and capital investment, including for the development of advanced manufacturing techniques and process controls. Manufacturers of biologic products often encounter difficulties in production, including difficulties with production costs and yields, quality control, including stability of the product, quality assurance testing, operator error and shortages of qualified personnel, as well as compliance with strictly enforced federal, state and foreign regulations. We cannot assure you that any stability or other issues relating to the manufacture of pegozafermin will not occur in the future. We have limited process development capabilities and have access only to external manufacturing capabilities. We do not have and we do not currently plan to acquire or develop the facilities or capabilities to manufacture bulk drug substance or filled drug product for use in human clinical trials or commercialization.

We face substantial competition, which may result in others discovering, developing or commercializing competing products before or more successfully than us.

The biopharmaceutical industry is intensely competitive and subject to rapid innovation and significant technological advancements. Our competitors include multinational pharmaceutical companies, specialized biotechnology companies, universities and other research institutions. A number of biotechnology and pharmaceutical companies are pursuing the development or marketing of pharmaceuticals that target the same diseases that we are targeting. Certain of these companies have recently published positive data regarding their clinical trials, which may further increase the competition we face. Smaller or earlier-stage companies may also prove to be significant competitors, particularly through collaborative arrangements with large, established companies. Given the high incidence of NASH and SHTG, it is likely that the number of companies seeking to develop products and therapies for the treatment of liver and cardio-metabolic diseases, such as NASH and SHTG, will increase.

There are numerous currently approved therapies for treating diseases other than NASH and some of these currently approved therapies may exert effects that could be similar to pegozafermin in NASH. Many of these approved drugs are well-established therapies or products and are widely accepted by physicians, patients and third-party payors. Some of these drugs are branded and subject to patent protection, and others are available on a generic basis. This may make it difficult for us to differentiate our products from currently approved therapies, which may adversely impact our business strategy. We expect that if pegozafermin or any future product candidates are approved, they will be priced at a significant premium over competitive generic products, including branded generic products. Insurers and other third-party payors may also encourage the use of generic products or specific branded products prior to utilization of pegozafermin. In addition, many companies are developing new therapeutics, and we cannot predict what the standard of care will be as pegozafermin or any future product candidates progress through clinical development. In addition, to the extent pegozafermin or any future product candidates are approved for liver or cardio-metabolic indications, such as SHTG, the commercial success of our products will also depend on our ability to demonstrate benefits over the then-prevailing standard of care, including diet, exercise and lifestyle modifications.

Further, if pegozafermin or any future product candidates are approved for the treatment of SHTG, we will compete with currently approved therapies and therapies further along in development. Our competitors both in the United States and abroad include large, well-established pharmaceutical and generic companies with significantly greater name recognition. Our competitors may be able to charge lower prices than we can, which may adversely affect our market acceptance. Many of these competitors have greater resources than we do, including financial, product development, marketing, personnel and other resources.

If our competitors market products that are more effective, safer or cheaper than our products or that reach the market sooner than our products, we may not achieve commercial success. Many of our competitors have substantially greater financial, technical, human and other resources than we do and may be better equipped to develop, manufacture and market technologically superior products. As a result, our competitors may obtain regulatory approval of their products more rapidly than we do or may obtain patent protection or other intellectual property rights that limit our ability to develop or commercialize our product candidate or any future product candidates. Our competitors may also develop and succeed in obtaining approval for drugs that are more effective, more convenient, more widely used and less costly or have a better safety profile than our products and these competitors may also be more successful than we are in manufacturing and marketing their products.

Unstable market and economic conditions, inflation, increases in interest rates, natural disasters, public health crises such as the COVID-19 pandemic, political crises, geopolitical events, such as the crisis in Ukraine, or other macroeconomic conditions, may have serious adverse consequences on our business and financial condition.

The global economy, including credit and financial markets, have experienced extreme volatility and disruptions at various points over the last few decades, including, among other things, diminished liquidity and credit availability, declines in consumer confidence, declines in economic growth, supply chain shortages, increases in inflation rates, higher interest rates, and uncertainty about economic stability. For example, the COVID-19 pandemic resulted in widespread unemployment, economic slowdown and extreme volatility in the capital markets. The Federal Reserve has raised interest rates multiple times in response to concerns about inflation and it may raise

them again. Higher interest rates, coupled with reduced government spending and volatility in financial markets, may increase economic uncertainty and affect consumer spending. Similarly, the ongoing military conflict between Russia and Ukraine and the rising tensions between China and Taiwan have created extreme volatility in the global capital markets and may have further global economic consequences, including disruptions of the global supply chain. Any such volatility and disruptions may adversely affect our business or the third parties on whom we rely. If the equity and credit markets deteriorate, including as a result of political unrest or war, it may make any necessary debt or equity financing more difficult to complete, more costly, 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 share price and could require us to delay or abandon development or commercialization plans. In addition, there is a risk that one or more of our service providers, manufacturers or other partners would not survive or be able to meet their commitments to us under such circumstances, which could directly affect our ability to attain our operating goals on schedule and on budget.

We have experienced and may in the future experience disruptions as a result of such macroeconomic conditions, including delays or difficulties in initiating or expanding clinical trials and manufacturing sufficient quantities of materials. Any one or a combination of these events could have a material and adverse effect on our results of operations and financial condition.

The 2023 Loan Agreement contains certain covenants that could adversely affect our operations and, if an event of default were to occur, we could be forced to repay any outstanding indebtedness sooner than planned and possibly at a time when we do not have sufficient capital to meet this obligation.

Pursuant to the 2023 Loan Agreement, we have pledged substantially all of our assets, other than our intellectual property rights, and have agreed that we may not sell or assign rights to our patents and other intellectual property without the prior consent of our lenders. Additionally, the 2023 Loan Agreement contains certain affirmative and negative covenants that could prevent us from taking certain actions without the consent of our lenders. These covenants may limit our flexibility in operating our business and our ability to take actions that might be advantageous to us and our stockholders. The 2023 Loan Agreement also includes customary events of default, including, among other things, an event of default upon a change of control. Upon the occurrence and continuation of an event of default, all amounts due under the 2023 Loan Agreement become automatically (in the case of a bankruptcy event of default) or may become (in the case of all other events of default and at the option of the administrative agent), immediately due and payable. If an event of default under the 2023 Loan Agreement should occur and be continuing, we could be required to immediately repay any outstanding indebtedness. If we are unable to repay such debt, the lenders would be able to foreclose on the secured collateral, including our cash accounts, and take other remedies permitted under the 2023 Loan Agreement. Even if we are able to repay such accelerated debt amount under the 2023 Loan Agreement upon an event of default, the repayment of these sums may significantly reduce our working capital and impair our ability to operate as planned.

We may encounter difficulties in managing our growth, which could adversely affect our operations.

We are in the early stages of building the full team that we anticipate we will need to complete the development pegozafermin and other future product candidates. As we advance our preclinical and clinical development programs for product candidates, seek regulatory approval in the United States and elsewhere and increase the number of ongoing product development programs, we anticipate that we will need to increase our product development, scientific and administrative headcount. We will also need to establish commercial capabilities in order to commercialize any product candidates that may be approved. Such an evolution may impact our strategic focus and our deployment and allocation of resources. Our ability to manage our operations and growth effectively depends upon the continual improvement of our procedures, reporting systems and operational, financial and management controls. We may not be able to implement administrative and operational improvements in an efficient or timely manner and may discover deficiencies in existing systems and controls. In addition, in order to continue to meet our obligations as a public company and to support our anticipated long-term growth, we will need to increase our general and administrative capabilities. Our management, personnel and systems may experience difficulty in adjusting to our growth and strategic focus.

We must attract and retain highly skilled employees in order to succeed. If we are not able to retain our current senior management team and our scientific advisors or continue to attract and retain qualified scientific, technical and business personnel, our business will suffer.

We may not be able to attract or retain qualified personnel and consultants due to the intense competition for such individuals in the biotechnology and pharmaceutical industries. If we are not able to attract and retain necessary personnel and consultants to accomplish our business objectives, it may significantly impede the achievement of our development and commercial objectives and our ability to implement our business strategy. In addition, we are highly dependent on the development, regulatory, manufacturing, commercialization and financial expertise of the members of our executive team, as well as other key employees and consultants. If we lose one or more of our executive officers or other key employees or consultants, our ability to implement our business strategy successfully could be seriously harmed.

We are developing new presentations for the liquid formulation of pegozafermin and we may be unsuccessful. Any changes in methods of product candidate manufacturing may result in the need to perform new clinical trials or obtain new drug product, which would require additional costs and cause delay.

We are developing a pre-filled syringe and plan to begin development of a pen-type autoinjector to deliver the liquid formulation of pegozafermin. Any formulation and presentation intended for commercialization is subject to regulatory approval. While the FDA has approved our new drug product formulation, there is no assurance that we will be successful in developing and receiving approval of a pre-filled syringe or an autoinjector on a timely basis or at all, any of which could impede our development and commercialization strategy for pegozafermin. In addition, there is no assurance comparable foreign regulatory authorities will approve our new drug product formulation. The FDA or other comparable foreign regulatory authorities could require nonclinical studies or clinical trials to support introduction of any new formulation, pre-filled syringe and autoinjector, which could delay completion of clinical trials, require the conduct of bridging clinical trials or the repetition of one or more clinical trials, increase our clinical trial costs, delay approval of pegozafermin and jeopardize our ability to commence product sales and generate revenue from pegozafermin, if approved.

We rely on third parties for certain aspects of our product candidate development process and we may not be able to obtain and maintain the third-party relationships that are necessary to develop, commercialize and manufacture some or all of our product candidates.

We expect to depend on collaborators, partners, licensees, clinical investigators, contract research organizations, manufacturers and other third parties to support our discovery efforts, to formulate product candidates, to conduct clinical trials for some or all of our product candidates, to manufacture clinical and commercial scale quantities of our drug substance and drug product and to market, sell and distribute any products we successfully develop. Any of these third parties may terminate their engagements with us at any time. If we need to enter into alternative arrangements, it would delay our product development activities and such alternative arrangements may not be available on terms acceptable to us. We also expect to rely on other third parties to store and distribute drug supplies for our clinical trials. Any performance failure on the part of our distributors could delay clinical development, marketing approval and/or commercialization of pegozafermin or any future product candidates, producing additional losses and depriving us of potential revenue.

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

Our operations, and those of our contract research organizations, CMO, suppliers, and other contractors and consultants, could be subject to earthquakes, power shortages, telecommunications failures, water shortages, floods, hurricanes, typhoons, fires, extreme weather conditions, acts of war, medical pandemics or epidemics, such as the novel coronavirus, and other natural or man-made disasters or business interruptions. The occurrence of any of these business disruptions could seriously harm our operations and financial condition and increase our costs and expenses.

If we fail to develop and commercialize additional product candidates, we may be unable to grow our business.

Although the development and commercialization of pegozafermin is currently our primary focus, as part of our longer-term growth strategy, we plan to evaluate the development and commercialization of other therapies related to NASH and other liver and cardio-metabolic diseases. The success of this strategy depends primarily upon our ability to identify and validate new therapeutic candidates, and to identify, develop and commercialize new drugs and biologics. Our research efforts may initially show promise in discovering potential new drugs and biologics yet fail to yield product candidates for clinical development for a number of reasons.

We may use our limited financial and human resources to pursue a particular research program or product candidate that is ultimately unsuccessful or less successful than other programs or product candidates that we may have forgone or delayed.

Because we have limited personnel and financial resources, we may forego or delay the development of certain programs or product candidates that later prove to have greater commercial potential than the programs or product candidates that we do pursue. Our resource allocation decisions may cause us to fail to capitalize on viable commercial products or profitable market opportunities. Our spending on current and future research and development programs for product candidates may not yield any commercially viable products. Similarly, our decisions to delay or terminate drug development programs may also be incorrect and could cause us to miss valuable opportunities.

We may seek to establish commercial collaborations for our product candidates, and, if we are not able to establish them on commercially reasonable terms, we may have to alter our development and commercialization plans.

Our drug development programs and the potential commercialization of our product candidates will require substantial additional cash to fund expenses. We may decide to collaborate with other pharmaceutical and biotechnology companies for the development and potential commercialization of our product candidates. Collaborations are complex and time-consuming to negotiate and document. We may not be able to negotiate collaborations on a timely basis, on acceptable terms, or at all. If we are unable to do so, we may have to curtail the development of the product candidate for which we are seeking to collaborate, reduce or delay its development program or one or more of our other development programs, delay its potential commercialization or reduce the scope of any sales or marketing activities or increase our expenditures and undertake development or commercialization activities at our own expense.

We may not be successful in our efforts to identify, in-license or acquire, discover, develop or commercialize additional product candidates.

We may seek to identify, in-license or acquire, discover, develop and commercialize additional product candidates. We cannot assure you that our effort to in-license or acquire additional product candidates will be successful. Even if we are successful in in-licensing or acquiring additional product candidates, their requisite development activities may require substantial resources, and we cannot assure you that these development activities will result in regulatory approvals.

Our international operations may expose us to business, regulatory, political, operational, financial, pricing and reimbursement risks associated with doing business outside of the United States.

Our use of our international facilities subjects us to U.S. and foreign governmental trade, import and export, and customs regulations and laws, including various economic and trade sanctions regulations administered by the U.S. Treasury Department’s Office of Foreign Assets Controls and the U.S. Export Administration Regulations. Compliance with these regulations and laws is costly and exposes us to penalties for non-compliance. Doing business internationally potentially involves a number of risks, any of which could harm our ongoing international clinical operations and supply chain, as well as any future international expansion and operations and, consequently, our business, financial condition, prospects and results of operations.

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

We face an inherent risk of product liability exposure related to the testing of our product candidates in human clinical trials and will face an even greater risk if we commercialize any resulting products. Product liability claims may be brought against us by subjects enrolled in our clinical trials, patients, or others using our products. Our clinical trial liability insurance coverage may not adequately cover all liabilities that we may incur.

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

We are exposed to the risk of fraud or other misconduct by our employees, contractors, vendors, principal investigators, consultants or future partners. Misconduct by these parties could include failures to comply with FDA regulations, to provide accurate information to the FDA, to comply with federal and state healthcare fraud and abuse laws and regulations, to report financial information or data timely, completely or accurately, or to disclose unauthorized activities to us. Most states also have statutes or regulations similar to these federal laws, which may apply to items such as pharmaceutical products and services reimbursed by private insurers. We and/or our future partners may be subject to administrative, civil and criminal sanctions for violations of any of these laws.

We depend on our information technology systems and those of our third-party collaborators, service providers, contractors or consultants. Our internal computer systems, or those of our third-party collaborators, service providers, contractors or consultants, may fail or suffer security breaches, disruptions, or incidents, which could result in a material disruption of our development programs or loss of data or compromise the privacy, security, integrity or confidentiality of sensitive information related to our business and have a material adverse effect on our reputation, business, financial condition or results of operations.

In the ordinary course of our business, we collect, store and transmit large amounts of confidential information, including intellectual property, proprietary business information and personal information. Our internal technology systems and infrastructure, and those of our current or future third-party collaborators, service providers, contractors and consultants are vulnerable to damage from computer viruses, unauthorized access or use resulting from malware, natural disasters, terrorism, war and telecommunication and electrical failures, denial-of-service attacks, cyber-attacks or cyber-intrusions over the Internet, hacking, phishing and other social engineering attacks, persons inside our organizations (including employees or contractors), loss or theft, or persons with access to systems inside our organization. From time to time, we are subject to periodic phishing attempts. In the third quarter of 2021, we discovered a business email compromise caused by phishing. The phishing attack did not result in the misappropriation of any funds and we do not believe that it had a material adverse effect on our business. We implemented remedial measures promptly following this incident, however, we cannot guarantee that our implemented remedial measures will prevent additional related, as well as unrelated, incidents. If a material system failure, accident or security breach were to occur and cause interruptions in our operations or the operations of third-party collaborators, service providers, contractors and consultants, it could result in a material disruption of our development programs and significant reputational, financial, legal, regulatory, business or operational harm.

To the extent that any real or perceived security breach affects our systems (or those of our third-party collaborators, service providers, contractors or consultants), or results in the loss of or accidental, unlawful or unauthorized access to, use of, release of, or other processing of personally identifiable information or damage to our data or applications or other data or applications relating to our technology or product candidates, or inappropriate disclosure of confidential or proprietary information, we could incur liabilities and the further development of our product candidates could be delayed. Any failure or perceived failure by us or any third-party collaborators, service providers, contractors or consultants to comply with our privacy, confidentiality, data security or similar obligations, or any data security incidents or other security breaches that result in the accidental, unlawful or unauthorized access to, use of, release of, processing of, or transfer of sensitive information, including personally identifiable information, may result in negative publicity, harm to our reputation, governmental investigations, enforcement actions, regulatory fines, litigation or public statements against us, could cause third parties to lose trust in us or could result in claims by third parties, including those that assert that we have breached our privacy,

confidentiality, data security or similar obligations, any of which could have a material adverse effect on our reputation, business, financial condition or results of operations.

Risks Related to Regulatory Approvals

Pegozafermin has not received regulatory approval. If we are unable to obtain regulatory approvals to market pegozafermin or any future product candidates, our business will be adversely affected.

We do not expect pegozafermin or any future product candidate to be commercially available for several years, if at all. Pegozafermin is and any future product candidate will be subject to strict regulation by regulatory authorities in the United States and in other countries. We cannot market any product candidate until we have completed all necessary preclinical studies and clinical trials and have obtained the necessary regulatory approvals. We do not know whether regulatory agencies will grant approval for pegozafermin or any future product candidate. Even if we complete preclinical studies and clinical trials successfully, we may not be able to obtain regulatory approvals or we may not receive approvals to make claims about our products that we believe to be necessary to effectively market our products. Data obtained from preclinical studies and clinical trials is subject to varying interpretations that could delay, limit or prevent regulatory approval, and failure to comply with regulatory requirements or inadequate manufacturing processes are examples of other problems that could prevent approval.

The regulatory authorities in the United States and the EU have not approved any products for the treatment of NASH, and while there are guidelines issued by the FDA for the development of drugs for the treatment of NASH, it is unclear whether the requirements for approval will change in the future or whether the FDA will rely on regulatory precedent for future regulatory approvals. Any such changes may require us to conduct new trials that could delay our timeframe and increase the costs of our programs related to pegozafermin or any future product candidate for the treatment of NASH or SHTG. In addition, we cannot be certain which efficacy endpoints or presentation thereof clinical or regulatory agencies may require in a Phase 3 clinical trial of NASH or for approval of our product candidates.

Even if we are able to obtain regulatory approvals for pegozafermin or any future product candidate, if they exhibit harmful side effects after approval, our regulatory approvals could be revoked or otherwise negatively impacted, and we could be subject to costly and damaging product liability claims.

Even if we receive regulatory approval for pegozafermin or any future product candidates, we will have tested them in only a small number of patients during our clinical trials. If our applications for marketing are approved and more patients begin to use our product, new risks and side effects associated with our products may be discovered. As a result, regulatory authorities may revoke their approvals. We have not had any discussions with the FDA regarding a surrogate endpoint or accelerated approval regulations. However, based on recent guidelines issued by the FDA for the development of drugs for the treatment of NASH, if pegozafermin is approved by the FDA based on a surrogate endpoint pursuant to section 506(c) of the Federal Food, Drug, and Cosmetic Act and the accelerated approval regulations (21 C.F.R. part 314, subpart H; 21 C.F.R. part 601, subpart E), consistent with FDA guidance, we will be required to conduct additional clinical trials establishing clinical benefit on the ultimate outcome of NASH. If pegozafermin is approved by the FDA for the treatment of SHTG based on an endpoint of the reduction of triglycerides, the FDA may still require a cardiovascular outcomes study as part of a post-marketing authorization commitment. Such a study would be time-consuming and costly and we cannot guarantee that we will see positive results, which could result in the revocation of the approval. Additionally, we may be required to conduct additional clinical trials, make changes in labeling of our product, reformulate our product or make changes and obtain new approvals for our and our suppliers' manufacturing facilities for pegozafermin and any future product candidates. We might have to withdraw or recall our products from the marketplace. We may also experience a significant drop in the potential sales of our product if and when regulatory approvals for such product are revoked. As a result, we may experience harm to our reputation in the marketplace or become subject to lawsuits, including class actions. Any of these results could decrease or prevent any sales of our approved product or substantially increase the costs and expenses of commercializing and marketing our product.

The regulatory approval processes of the FDA and comparable foreign regulatory authorities are lengthy, time-consuming and inherently unpredictable. Our inability to obtain regulatory approval for pegozafermin or any future product candidates would substantially harm our business.

Currently, we do not have any product candidates that have received regulatory approval. The time required to obtain approval from the FDA and comparable foreign regulatory authorities is unpredictable but typically takes many years following the commencement of preclinical studies and clinical trials and depends upon numerous factors, including the substantial discretion of the regulatory authorities. In addition, approval policies, regulations or the type and amount of clinical data necessary to gain approval may change during the course of a product candidate's development and may vary among jurisdictions. It is possible that none of pegozafermin or any future product candidates will ever obtain regulatory approval. Pegozafermin or any future product candidate could fail to receive regulatory approval from the FDA or comparable foreign regulatory authorities for many reasons, including those referenced in Part I, Item 1. "Business-Government Regulation and Product Approval" in this Annual Report on Form 10-K. If we were to obtain approval, regulatory authorities may approve any of our product candidates for fewer or more limited indications than we request, may grant approval contingent on the performance of costly post-marketing clinical trials or may approve a product candidate with a label that does not include the labeling claims necessary or desirable for the successful commercialization of the product candidate.

Even if pegozafermin or any future product candidate receives regulatory approval, it may still face future development and regulatory difficulties.

Even if we obtained regulatory approval for a product candidate, it would be subject to ongoing requirements by the FDA and comparable foreign regulatory authorities governing the manufacture, quality control, further development, labeling, packaging, storage, distribution, safety surveillance, import, export, advertising, promotion, recordkeeping and reporting of safety and other post-market information. In addition, manufacturers of drug products and their facilities are subject to continual review and periodic inspections by the FDA and other regulatory authorities for compliance with cGMP, regulations and standards. If we or a regulatory agency discover previously unknown problems with a product, such as adverse events of unanticipated severity or frequency, or problems with the facility where the product is manufactured, a regulatory agency may impose restrictions on that product, the manufacturing facility or us, including requiring recall or withdrawal of the product from the market or suspension of manufacturing. If we, our product candidates or the manufacturing facilities for our product candidates fail to comply with applicable regulatory requirements, or undesirable side effects caused by such products are identified, a regulatory agency may: issue safety alerts, Dear Healthcare Provider letters, press releases or other communications containing warnings about such product; mandate modifications to promotional materials or require us to provide corrective information to healthcare practitioners; require that we conduct post-marketing studies; require us to enter into a consent decree, which can include imposition of various fines, reimbursements for inspection costs, required due dates for specific actions and penalties for noncompliance; seek an injunction or impose civil or criminal penalties or monetary fines; suspend marketing of, withdraw regulatory approval of or recall such product; suspend any ongoing clinical studies; refuse to approve pending applications or supplements to applications filed by us; suspend or impose restrictions on operations, including costly new manufacturing requirements; or seize or detain products, refuse to permit the import or export of products or require us to initiate a product recall. The occurrence of any event or penalty described above may inhibit our ability to commercialize our products and generate product revenue.

Current and future legislation may increase the difficulty and cost for us, and any collaborators, to obtain marketing approval of and commercialize our drug candidates and affect the prices we, or they, may obtain.

Heightened governmental scrutiny over the manner in which manufacturers set prices for their marketed products 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. 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 therapies, which could result in reduced demand for our product candidates or additional pricing pressures. Most recently, on August 16, 2022, President Biden signed into law the Inflation Reduction Act of 2022 ("IRA"), which, among other provisions, included several measures intended to lower the cost of prescription drugs and related healthcare reforms. We cannot be sure whether additional legislation or rulemaking related to the IRA will be issued or enacted, or what impact, if any, such changes will have on the profitability of any of our drug candidates, if approved for commercial use, in the future.

Healthcare insurance coverage and reimbursement may be limited or unavailable for our product candidate, if approved, which could make it difficult for us to sell our product candidate or other therapies profitably.

The success of pegozafermin, if approved, depends on the availability of coverage and adequate reimbursement from third-party payors including governmental healthcare programs, such as Medicare and Medicaid, commercial payors, and health maintenance organizations. We cannot be sure that coverage and reimbursement will be available for, or accurately estimate the potential revenue from, our product candidates or assure that coverage and reimbursement will be available for any product that we may develop.

Governments outside the United States tend to impose strict price controls, which may adversely affect our revenue, if any.

In some countries, particularly the countries of the European Union, the pricing of prescription pharmaceuticals is subject to governmental control. In these countries, pricing negotiations with governmental authorities can take considerable time after the receipt of marketing approval for a drug. In addition, there can be considerable pressure by governments and other stakeholders on prices and reimbursement levels, including as part of cost containment measures. Political, economic and regulatory developments may further complicate pricing negotiations. To obtain coverage and reimbursement or pricing approval in some countries, we may be required to conduct a clinical trial that compares the cost-effectiveness of our drug candidate to other available procedures. If reimbursement of our drugs is unavailable or limited in scope or amount, or if pricing is set at unsatisfactory levels, our business could be harmed, possibly materially.

Risks Relating to Intellectual Property

Our success depends upon our ability to obtain and maintain intellectual property protection for our products and technologies.

Our success will depend in significant part on our current or future licensors', licensees' or collaborators' ability to establish and maintain adequate protection of our owned and licensed intellectual property covering the product candidates we plan to develop, and the ability to develop these product candidates and commercialize the products resulting therefrom, without infringing the intellectual property rights of others. In addition to taking other steps to protect our intellectual property, we hold issued patents, we have applied for patents, and we intend to continue to apply for patents, with claims covering our technologies, processes and product candidates when and where we deem it appropriate to do so. We have filed numerous patent applications both in the United States and in certain foreign jurisdictions to obtain patent rights to inventions we have discovered, with claims directed to compositions of matter, methods of use and other technologies relating to our programs. There can be no assurance that any of these patent applications will issue as patents or, for those applications that do mature into patents, that the claims of the patents will exclude others from making, using or selling our product candidates or products that compete with or are similar to our product candidates. In countries where we have not sought and do not seek patent protection, third parties may be able to manufacture and sell our product candidates without our permission, and we may not be able to stop them from doing so.

With respect to patent rights, we do not know whether any of the pending patent applications for any of our product candidates will result in the issuance of patents that effectively protect our technologies, processes and product candidates, or if any of our issued patents or our current or future licensors', licensees' or collaborators' issued patents will effectively prevent others from commercializing competitive technologies, processes and products. We cannot be certain that we or our current or future licensors, licensees or collaborators were the first to make the inventions claimed in our owned or licensed patents or pending patent applications, or that we or our current or future licensors, licensees or collaborators were the first to file for patent protection of such inventions.

Any changes we make to our pegozafermin or any future product candidates to cause them to have what we view as more advantageous properties may not be covered by our existing patents and patent applications, and we may be required to file new applications and/or seek other forms of protection for any such altered product candidates. The patent landscape surrounding the technology underlying our product candidates is crowded, and there can be no assurance that we would be able to secure patent protection that would adequately cover an alternative to pegozafermin or any future product candidates.

We and our current or future licensors, licensees or collaborators may not be able to prepare, file and prosecute all necessary or desirable patent applications at a reasonable cost or in a timely manner. It is also possible that we or our current or future licensors, licensees or collaborators will fail to identify patentable aspects of inventions made in the course of development and commercialization activities before it is too late to obtain patent protection for them. Moreover, in some circumstances, we may not have the right to control the preparation, filing and prosecution of patent applications, or to maintain or enforce the patents, covering technology that we license from or license to third parties and may be reliant on our current or future licensors, licensees or collaborators to perform these activities, which means that these patent applications may not be prosecuted, and these patents enforced, in a manner consistent with the best interests of our business. If our current or future licensors, licensees or collaborators fail to establish, maintain, protect or enforce such patents and other intellectual property rights, such rights may be reduced or eliminated. If our current or future licensors, licensees or collaborators are not fully cooperative or disagree with us as to the prosecution, maintenance or enforcement of any patent rights, such patent rights could be compromised.

Similar to the patent rights of other biotechnology companies, the scope, validity and enforceability of our owned and licensed patent rights generally are highly uncertain and involve complex legal and factual questions. 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. In recent years, these areas have been the subject of much litigation in the industry. As a result, the issuance, scope, validity, enforceability and commercial value of our and our current or future licensors', licensees' or collaborators' patent rights are highly uncertain. Our and our current or future licensors', licensees' or collaborators' pending and future patent applications may not result in patents being issued that protect our technology or product candidates, or products

resulting therefrom, in whole or in part, or that effectively prevent others from commercializing competitive technologies and products. The patent examination process may require us or our current or future licensors, licensees or collaborators to narrow the scope of the claims of pending and future patent applications, which would limit the scope of patent protection that is obtained, if any. Our and our current or future licensors', licensees' or collaborators' patent applications cannot be enforced against third parties practicing the technology that is currently claimed in such applications unless and until a patent issues from such applications, and then only to the extent the claims that issue are broad enough to cover the technology being practiced by those third parties.

Furthermore, 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 the resulting products are commercialized. As a result, our owned and in-licensed patents may not provide us with sufficient rights to exclude others from commercializing products similar or identical to ours. We expect to seek extensions of patent terms for our issued patents, where available. The applicable authorities, including the FDA in the United States, and any comparable foreign regulatory authorities, may not agree with our assessment of whether such extensions are available, and may refuse to grant extensions to our patents, or may grant more limited extensions than we request. In addition, we may not be granted an extension because of, for example, failing to apply within applicable deadlines, failing to apply prior to the expiration of relevant patents or otherwise failing to satisfy applicable requirements.

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

The legal protection afforded to inventors and owners of intellectual property in countries outside of the United States may not be as protective or effective as that in the United States and we may, therefore, be unable to acquire and enforce intellectual property rights outside the United States to the same extent as in the United States. Whether filed in the United States or abroad, our patent applications may be challenged or may fail to result in issued patents. Filing, prosecuting, enforcing and defending patents on product candidates in all countries throughout the world would be prohibitively expensive, and our intellectual property rights in some countries outside the United States are less extensive than those in the United States. In addition, the laws of some foreign countries do not protect intellectual property rights to the same extent as federal and certain state laws in 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 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 pegozafermin or any future product candidates and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing.

We rely on a license from Teva and a sublicense from ratiopharm to patents and know-how related to glycoPEGylation technology that are used in the development, manufacture and commercialization of* pegozafermin*. Any termination or loss of significant rights, including the right to glycoPEGylation technology, or breach, under these agreements or any future license agreement related to our product candidates, would materially and adversely affect our ability to continue the development and commercialization of the related product candidates.

In April 2018, we entered into an Asset Transfer and License Agreement (the "FGF21 Agreement") with Teva under which we acquired certain patents, intellectual property and other assets relating to Teva's glycoPEGylated FGF21 program, including pegozafermin. Under this agreement, we were granted a perpetual, non-exclusive (but exclusive as to pegozafermin), non-transferable, worldwide license to patents and know-how related to glycoPEGylation technology used in the development, manufacture and commercialization of pegozafermin and products containing pegozafermin. The FGF21 Agreement also contains numerous covenants with which we must comply, including the utilization of commercially reasonable efforts to develop and ultimately commercialize pegozafermin, as well as certain reporting covenants and the obligation to make royalty payments, if and when pegozafermin is approved for commercialization. Our failure to satisfy any of these covenants could result in the termination of the FGF21 Agreement. In addition, we entered into a Sublicense Agreement with ratiopharm (the "ratiopharm Sublicense"), under which we were granted a perpetual, exclusive, worldwide sublicense to patents and know-how related to glycoPEGylation technology used in the development, manufacture and commercialization of pegozafermin and products containing pegozafermin. Termination of the FGF21 Agreement or the ratiopharm Sublicense will impact our rights under the intellectual property licensed to us by Teva and ratiopharm, respectively, including our license to glycoPEGylation technology, but will not affect our rights under the assets assigned to us.

Beyond this agreement, our commercial success will also depend upon our ability, and the ability of our licensors, to develop, manufacture, market and sell our product candidates and use our proprietary technologies without infringing the proprietary rights of third parties. A third party may hold intellectual property rights, including patent rights, that are important or necessary to the development of our product candidates. As a result, we may enter into additional license agreements in the future. If we fail to comply with the obligations under these agreements, including payment and diligence obligations, our licensors may have the right to terminate these agreements, in which event we may not be able to develop, manufacture, market or sell any product that is covered by these agreements or to engage in any other activities necessary to our business that require the freedom to operate afforded by the agreements, or we may face other penalties under the agreements.

We may be unable to obtain intellectual property rights or technology necessary to develop and commercialize pegozafermin and any future product candidates.

The patent landscape around our programs is complex, and we are aware of several third-party patents and patent applications containing subject matter that might be relevant to pegozafermin. Depending on what claims ultimately issue from these patent applications, and how courts construe the issued patent claims, as well as depending on the ultimate formulation and method of use of pegozafermin or any future product candidates, we may need to obtain a license to practice the technology claimed in such patents. There can be no assurance that such licenses will be available on commercially reasonable terms, or at all.

We may become involved in lawsuits or other proceedings to protect or enforce our intellectual property, which could be expensive, time-consuming and unsuccessful and have a material adverse effect on the success of our business.

Third parties may infringe our patents or misappropriate or otherwise violate our intellectual property rights. In the future, we may initiate legal proceedings to enforce or defend our intellectual property rights, to protect our trade secrets or to determine the validity or scope of intellectual property rights we own or control. Also, third parties may initiate legal proceedings against us to challenge the validity or scope of intellectual property rights we own, control or to which we have rights. An adverse result in any litigation proceeding could put one or more of our patents at risk of being invalidated, narrowed, held unenforceable or interpreted in such a manner that would not preclude third parties from entering the market with competing products.

Third-party pre-issuance submission of prior art to the USPTO, or opposition, derivation, revocation, reexamination, *inter partes* review or interference proceedings, or other pre-issuance or post-grant proceedings or other patent office proceedings or litigation in the United States or other jurisdictions provoked by third parties or brought by us, may be necessary to determine the inventorship, priority, patentability or validity of inventions with respect to our patents or patent applications. An unfavorable outcome could leave our technology or product candidates without patent protection, allow third parties to commercialize our technology or product candidates and compete directly with us, without payment to us, or could require us to obtain license rights from the prevailing party in order to be able to manufacture or commercialize our product candidates without infringing third-party patent rights. Our business could be harmed if the prevailing party in such a case does not offer us a license on commercially reasonable terms, or at all. Even if we obtain a license, it may be non-exclusive, thereby giving our competitors access to the same technologies licensed to us. In addition, if the breadth or strength of protection provided by our patents and patent applications is threatened, it could dissuade companies from collaborating with us to license, develop or commercialize current or future product candidates. Even if we successfully defend such litigation or proceeding, we may incur substantial costs and our defense may distract our management and other employees.

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. In addition, many foreign jurisdictions have rules of discovery that are different than those in the United States and that may make defending or enforcing our patents extremely difficult. There could also be public announcements of the results of hearings, motions or other interim proceedings or developments. If securities analysts or investors perceive these results to be negative, it could have a material adverse effect on the price of shares of our common stock.

Third parties may initiate legal proceedings against us alleging that we infringe their intellectual property rights or we may initiate legal proceedings against third parties to challenge the validity or scope of intellectual property rights controlled by third parties.

Third parties may initiate legal proceedings against us alleging that we infringe their intellectual property rights or we may initiate legal proceedings against third parties to challenge the validity or scope of intellectual property rights controlled by third parties, including in oppositions, interferences, revocations, reexaminations, *inter partes* review or derivation proceedings before the USPTO or its counterparts in other jurisdictions. These proceedings can be expensive and time-consuming and many of our adversaries in these proceedings may have the ability to dedicate substantially greater resources to prosecuting these legal actions than we can. We could be found liable for monetary damages, including treble damages and attorneys' fees, if we are found to have willfully infringed a patent of a third party. A finding of infringement could prevent us from commercializing our pegozafermin or any future product candidates or force us to cease some of our business operations, which could materially harm our business.

Although we have reviewed certain third-party patents and patent filings that we believe may be relevant to our therapeutic candidates or products, we have not conducted a freedom-to-operate search or analysis for any of our therapeutic candidates or products, and we may not be aware of patents or pending or future patent applications that, if issued, would block us from commercializing our product candidates. Thus, we cannot guarantee that our product candidates, or our commercialization thereof, do not and will not infringe any third party's intellectual property.

Risks Related to Ownership of Our Common Stock

The price of our common stock may be volatile, and you may lose all or part of your investment.

The market price of our common stock could fluctuate significantly, and you may not be able to resell your shares at or above the price you paid for your shares. Those fluctuations could be based on various factors in addition to those otherwise described in this Annual Report on Form 10-K, including those described in these "Risk Factors." Any of these factors may result in large and sudden changes in the volume and trading price of our common stock. In the past, following periods of volatility in the market price of a company's securities, stockholders have often instituted securities class action litigation against that company.

Sales of our common stock, or the perception that such sales may occur, or issuance of shares of our common stock upon exercise of warrants could depress the price of our common stock.

Sales of a substantial number of shares of our common stock in the public market, or the perception that such sales may occur, could depress the market price of our common stock. Certain holders of shares of our common stock have rights, subject to certain conditions, to require us to file registration statements covering their shares or to include their shares in registration statements that we may file for ourselves or other stockholders. In addition, we have filed a registration statement registering under the Securities Act the shares of our common stock reserved for issuance under our 2019 Equity Incentive Plan, including shares issuable upon exercise of outstanding options. These shares can be freely sold in the public market upon issuance, subject to volume limitations applicable to affiliates. Further, as opportunities present themselves, we may enter into financing or similar arrangements in the future, including the issuance of debt or equity securities.

In addition, we must settle exercises of our outstanding warrants in shares of our common stock. The issuance of shares of our common stock upon exercise of the warrants will dilute the ownership interests of our stockholders, which could depress the trading price of our common stock. In addition, the market's expectation that exercises may occur could depress the trading price of our common stock even in the absence of actual exercises. Moreover, the expectation of exercises could encourage the short selling of our common stock, which could place further downward pressure on the trading price of our common stock.

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

Existing stockholders could suffer dilution or be negatively affected by fixed payment obligations we may incur if we raise additional funds through the issuance of additional equity securities, including under the ATM Facility (defined below), or debt. Furthermore, these securities may have rights senior to those of our common stock and could contain covenants or protective rights that would restrict our operations and potentially impair our competitiveness, such as limitations on our ability to incur additional debt, limitations on our ability to acquire, sell or license intellectual property rights and other operating restrictions that could adversely impact our ability to conduct our business.

Hedging activity by investors in the warrants could depress the trading price of our common stock.

We expect that many investors in our warrants will seek to employ an arbitrage strategy. Under this strategy, investors typically short sell a certain number of shares of our common stock and adjust their short position over time while they continue to hold the warrants. Investors may also implement this type of strategy by entering into swaps on our common stock in lieu of, or in addition to, short selling shares of our common stock. This market activity, or the market's perception that it will occur, could depress the trading price of our common stock.

General Risk Factors

Our directors, executive officers and current holders of 5% or more of our capital stock have substantial control over our company, which could limit your ability to influence the outcome of matters subject to stockholder approval, including a change of control.

As of December 31, 2022, our executive officers, directors and other holders of 5% or more of our common stock beneficially owned a majority of our outstanding common stock. As a result, our executive officers, directors and other holders of 5% or more of our common stock, if they act, will be able to influence or control matters requiring approval by our stockholders, including the election of directors and the approval of mergers, acquisitions or other extraordinary transactions. In addition, our current directors, executive officers and other holders of 5% or more of our common stock, acting together, would have the ability to control the management and affairs of our company. They may also have interests that differ from yours and may vote in a way with which you disagree and that may be adverse to your interests. This concentration of ownership may have the effect of delaying, preventing or deterring a change of control of our company, could deprive our stockholders of an opportunity to receive a premium for their shares of our common stock as part of a sale of our company.

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

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.

These inherent limitations include the realities that judgments in decision-making can be faulty, and that breakdowns can occur because of simple error or mistake. Additionally, controls can be circumvented by the individual acts of some persons, by collusion of two or more people or by an unauthorized override of the controls. Accordingly, because of the inherent limitations in our control system, misstatements due to error or fraud may occur and not be detected.

Our amended and restated certificate of incorporation, amended and restated bylaws and Delaware law could prevent a third party from acquiring us (even if an acquisition would benefit our stockholders), may limit the ability of our stockholders to replace our management and limit the price that investors might be willing to pay for shares of our common stock.

Our amended and restated certificate of incorporation and our amended and restated bylaws could have the effect of making it more difficult for a third party to acquire, or of discouraging a third party from attempting to acquire, control of us. These provisions could delay or prevent a change in control of the Company and could limit the price that investors might be willing to pay in the future for shares of our common stock. In addition, as a Delaware corporation, we are subject to the anti-takeover provisions of Section 203 of the Delaware General Corporation Law, which prohibits a Delaware corporation from engaging in a business combination specified in the statute with an interested stockholder (as defined in the statute) for a period of three years after the date of the transaction in which the person first becomes an interested stockholder, unless the business combination is approved in advance by a majority of the independent directors or by the holders of at least two-thirds of the outstanding disinterested shares. The application of Section 203 of the Delaware General Corporation Law could also have the effect of delaying or preventing a change of control of us.

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

Our amended and restated certificate of incorporation provides that the Court of Chancery of the State of Delaware is the exclusive forum for certain actions or proceedings under Delaware statutory or common law. Our amended and restated certificate of incorporation provides further that the federal district courts of the United States will be the exclusive forum for resolving any complaint asserting a cause of action arising under the Securities Act. 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. If a court were to find the choice of forum provision contained in our amended and restated certificate of incorporation to be inapplicable or unenforceable, we may incur additional costs associated with resolving such action in other jurisdictions.

Our ability to use our net operating loss carryforwards and other tax attributes may be limited.

As of December 31, 2022, we had U.S. federal and state net operating loss ("NOL") carryforwards of $160.9 million and $169.8 million, respectively, which may be available to offset future taxable income. As of December 31, 2022, we also had gross federal tax credits of $4.3 million, which may be used to offset future tax liabilities. These NOLs and tax credit carryforwards will begin to expire in 2040. Use of our NOL carryforwards and tax credit carryforwards depends on many factors, including having current or future taxable income, which cannot be assured. In addition, the Company is currently under examination by the Israeli tax authorities for 2018 and 2019, which could impact our NOL carryforwards.

Item 1B. Unresolved Staff Comments.

None.

Item 2. Properties.

We lease office space at 142 Sansome Street, San Francisco, California 94104, which consists of approximately 3,600 square feet. This lease expires on January 14, 2025. We believe that our current space is adequate for our needs. We also believe we will be able to obtain additional space, as needed, on commercially reasonable terms.

Item 3. Legal Proceedings.

We are currently not a party to any material legal proceedings. From time to time, we may become involved in legal proceedings arising in the ordinary course of our business. Regardless of outcome, litigation can have an adverse impact on us due to defense and settlement costs, diversion of management resources, negative publicity, reputational harm 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 is traded on The Nasdaq Global Market under the symbol "ETNB."

As of March 3, 2023, there were approximately 6 stockholders of record of our common stock. Since many of our shares of common stock are held by brokers and other institutions on behalf of stockholders, we are unable to estimate the total number of stockholders represented by these record holders.

Dividend Policy

We have never declared or paid cash dividends on our capital stock and have no present intention to pay cash dividends on our common stock for the foreseeable future. Any determination to pay dividends to holders of our common stock will be at the discretion of our board of directors and will depend on many factors, including our financial condition, results of operations, liquidity, earnings, projected capital and other cash requirements, legal requirements, restrictions in the agreements governing any indebtedness we may enter into, business prospects and other factors that our board of directors deems relevant.

Item 6. [Reserved].

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

You should read the following discussion and analysis of our financial condition and results of operations together with our consolidated financial statements and related notes and other financial information included elsewhere in this Annual Report on Form 10-K. Some of the information contained in this discussion and analysis includes forward-looking statements that involve risks and uncertainties. Our actual results could differ materially from those described in or implied by these forward-looking statements. Factors that could cause or contribute to such differences include, but are not limited to, those identified below and those discussed in the section titled "Risk Factors" included elsewhere in this Annual Report on Form 10-K.

Overview

We are a clinical-stage biopharmaceutical company focused on the development and commercialization of innovative therapies for the treatment of liver and cardio-metabolic diseases. Our lead product candidate, pegozafermin (previously BIO89-100), a specifically engineered glycoPEGylated analog of fibroblast growth factor 21 ("FGF21"), is currently being developed for the treatment of nonalcoholic steatohepatitis ("NASH") and for the treatment of severe hypertriglyceridemia ("SHTG"). NASH is a severe form of nonalcoholic fatty liver disease ("NAFLD"), characterized by inflammation and fibrosis in the liver that can progress to cirrhosis, liver failure, hepatocellular carcinoma ("HCC") and death. There are currently no approved products for the treatment of NASH. In 2020 and 2022, we presented positive topline results from cohorts 1 through 6 and cohort 7 respectively, in our Phase 1b/2a trial of pegozafermin in NASH patients which has informed the advancement of our clinical strategy in NASH. We initiated a Phase 2b trial (ENLIVEN) evaluating pegozafermin in fibrosis stage 2 or 3 NASH patients in June 2021. In the ENLIVEN trial, patients receive weekly doses or an every two-week dose of pegozafermin or placebo for 24 weeks followed by a blinded extension phase of an additional 24 weeks for a total treatment period of 48 weeks. ENLIVEN completed enrollment in August 2022 and we are expecting to report topline data from this trial in March 2023. In 2021, we completed a pharmacokinetic study of pegozafermin in NASH patients with compensated cirrhosis (fibrosis stage F4) demonstrating that a 30 mg dose of pegozafermin has similar single-dose pharmacokinetics and pharmacodynamics in F4 as it does in non-cirrhotic NASH. We are currently evaluating the potential opportunity for pegozafermin in these fibrosis stage F4 patients. We are also developing pegozafermin for the treatment of SHTG. In June 2022, we announced positive topline results from the ENTRIGUE Phase 2 trial of pegozafermin in SHTG patients. SHTG is a condition identified by severely elevated levels of triglycerides (≥500 mg/dL), which is associated with an increased risk of NASH, cardiovascular events and acute pancreatitis. The trial met its primary endpoint demonstrating statistically significant and clinically meaningful reductions in triglycerides from baseline and key secondary endpoints. We have received feedback from the FDA supporting the advancement of pegozafermin into Phase 3 and are planning to initiate the first of two recommended Phase 3 trials in the second quarter of 2023. In parallel, we have developed plans to optimize our clinical development program across both indications that would leverage the safety database from our SHTG Phase 3 program to support our NASH program. We expect to finalize these plans after we have reviewed results from the ENLIVEN trial.

We commenced operations in 2018 and have devoted substantially all of our resources to raising capital, acquiring our initial product candidate, identifying and developing pegozafermin, licensing certain related technology, conducting research and development activities (including preclinical studies and clinical trials) and providing general and administrative support for these operations.

As of December 31, 2022, our cash and cash equivalents and short-term available-for-sale securities totaled $188.2 million. Based on our current operating plan, we believe that our cash and cash equivalents and short-term available-for-sale securities as of December 31, 2022, together with the proceeds received in January and February 2023 from our ATM Facility (defined below) and the 2023 Loan Agreement (defined below), will be sufficient to meet our anticipated cash requirements for a period of at least one year from the date this Annual Report on Form 10-K is filed with the Securities and Exchange Commission ("SEC").

We have incurred net losses since our inception. Our net losses for the year ended December 31, 2022 and 2021 were $102.0 million and $90.1 million, respectively. As of December 31, 2022, we had an accumulated deficit of $315.2 million. We expect to continue to incur significant expenses and increasing operating losses as we advance pegozafermin and any future product candidates through clinical trials, seek regulatory approval for pegozafermin and any future product candidates, expand our clinical, regulatory, quality, manufacturing and

commercialization capabilities, protect our intellectual property, prepare for and, if approved, proceed to commercialization of pegozafermin and any future product candidates, expand our general and administrative support functions, including hiring additional personnel, and incur additional costs associated with operating as a public company. Our net losses may fluctuate significantly from quarter-to-quarter and year-to-year, depending on the timing of our clinical trials and our expenditures on other research and development activities.

Ongoing COVID-19 Pandemic

The ongoing COVID-19 pandemic has disrupted and may continue to disrupt our business and delay our development timeline. The extent to which the COVID-19 pandemic may impact our future operating results and financial condition is uncertain. For more information regarding risks related to the ongoing COVID-19 pandemic, please see the risk factor entitled "The ongoing COVID-19 pandemic has resulted and may in the future result in significant disruptions to our clinical trials or other business operations, which could have a material adverse effect on our business," in Part I, Item 1A of this Annual Report on Form 10-K.

Components of Results of Operations

Research and Development Expenses

Research and development expenses consist primarily of costs incurred for the development of our lead product candidate, pegozafermin. Our research and development expenses consist primarily of external costs related to preclinical and clinical development, including costs related to acquiring patents and intellectual property, expenses incurred under license agreements and agreements with contract research organizations and consultants, costs related to acquiring and manufacturing clinical trial materials, including under agreements with contract manufacturing organizations and other vendors, costs related to the preparation of regulatory submissions and expenses related to laboratory supplies and services, as well as personnel costs. Personnel costs consist of salaries, employee benefits and stock-based compensation for individuals involved in research and development efforts.

We expense all research and development expenses in the periods in which they are incurred. We accrue for costs incurred as services are provided by monitoring the status of specific activities and invoices received from our external service providers. We adjust our accrued expenses as actual costs become known.

Payments associated with licensing agreements to acquire licenses to develop, use, manufacture and commercialize products that have not reached technological feasibility and do not have alternate commercial use are expensed as incurred. Where contingent milestone payments are due to third parties under research and development arrangements or license agreements, the milestone payment obligations are expensed when the milestone results are probable and estimable, which is generally upon achievement of milestones.

We expect our research and development expenses to increase for the foreseeable future as we continue the development of pegozafermin and continue to invest in research and development activities. The process of conducting the necessary clinical research to obtain regulatory approval is costly and time-consuming, and the successful development of pegozafermin and any future product candidates is highly uncertain. To the extent that pegozafermin continues to advance into larger and later stage clinical trials, our expenses will increase substantially and may become more variable. The actual probability of success for pegozafermin or any future product candidate may be affected by a variety of factors, including the safety and efficacy of our product candidates, investment in our clinical programs, manufacturing capability and competition with other products. As a result, we are unable to determine the timing of initiation, duration and completion costs of our research and development efforts or when and to what extent we will generate revenue from the commercialization and sale of pegozafermin or any future product candidate.

General and Administrative Expenses

General and administrative expenses consist primarily of personnel costs, expenses for outside professional services, including legal, human resource, audit and accounting services, consulting costs and allocated facilities costs. Personnel and related costs consist of salaries, employee benefits and stock-based compensation for personnel in executive, finance, commercial and other administrative functions. Facilities costs consist of rent and maintenance

of facilities. We expect our general and administrative expenses to increase for the foreseeable future as we increase the size of our administrative function to support the growth of our business and support our continued research and development activities.

Interest Expense

Interest expense consists of interest expense, accretion of final payment fees and amortization of deferred debt issuance costs related to our term loan facility.

Interest Income and Other, Net

Interest income and other, net primarily consists of interest income including accretion of discount on available-for-sale securities, offset by amortization of premium on available-for-sale securities.

Results of Operations

Year Ended December 31, 2022 and 2021

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

	Year Ended December 31,		
	2022	2021	Change
Operating expenses:			
Research and development	$ 80,796	$ 70,330	$ 10,466
General and administrative	21,453	19,413	2,040
Total operating expenses	102,249	89,743	12,506
Loss from operations	(102,249)	(89,743)	(12,506)
Interest expense	(1,922)	(674)	(1,248)
Interest income and other, net	2,164	148	2,016
Income tax (expense) benefit	(19)	147	(166)
Net loss	$ (102,026)	$ (90,122)	$ (11,904)

Research and Development Expenses

The following table summarizes the period-over-period changes in research and development expenses for the periods presented (in thousands):

	Year Ended December 31,		
	2022	2021	Change
Clinical development	$ 44,683	$ 29,500	$ 15,183
Contract manufacturing	19,515	27,584	(8,069)
Personnel-related expenses	15,156	11,725	3,431
Preclinical costs	—	66	(66)
Other expenses	1,442	1,455	(13)
Total research and development expenses	$ 80,796	$ 70,330	$ 10,466

Research and development expenses increased by $10.5 million, or 15%, to $80.8 million, for the year ended December 31, 2022 compared to $70.3 million for the year ended December 31, 2021. The change was primarily due to an increase of $15.2 million in clinical development costs related to our ongoing clinical trials and an increase of $3.4 million in personnel-related costs due to higher headcount and stock-based compensation, partially offset by a $8.1 million decrease in contract manufacturing costs, mainly as a result of the completion of the manufacture of batches to cater to our current supply requirements for our ongoing clinical trials.

General and Administrative Expenses

General and administrative expenses increased by $2.0 million, or 11%, to $21.5 million, for the year ended December 31, 2022 compared to $19.4 million for the year ended December 31, 2021. The change was primarily due to an increase of $1.7 million in personnel-related costs, due to higher headcount and stock-based compensation and an increase of $0.5 million in professional services primarily due to consulting services, partially offset by a decrease of $0.2 million in insurance related costs.

Interest Expense

Interest expense increased by $1.2 million, or 185%, to $1.9 million, for the year ended December 31, 2022 compared to $0.7 million for the year ended December 31, 2021, primarily due to a larger outstanding balance on our term loan facility during the year ended December 31, 2022 as compared to the year ended December 31, 2021, as well as higher interest rates and higher accretion of the final payment fee and amortization of debt issuance costs during the year ended December 31, 2022.

Interest Income and Other, Net

Interest income and other, net increased by $2.0 million to $2.2 million, for the year ended December 31, 2022 compared to $0.1 million, for the year ended December 31, 2021, primarily due to higher cash equivalents and short-term available-for-sale securities in the latter half of 2022 compared to 2021, as well as the impact of favorable interest rates in 2022.

Liquidity and Capital Resources

To date, we have incurred significant net losses and negative cash flows from operations. As of December 31, 2022, we had available cash and cash equivalents and short-term available-for-sale securities of $188.2 million and an accumulated deficit of $315.2 million.

In March 2021, we entered into a sales agreement (as amended, the "Sales Agreement") with SVB Securities LLC and Cantor Fitzgerald & Co. (the "Sales Agents") pursuant to which we may offer and sell up to $75.0 million of shares of our common stock, from time to time, in "at-the-market" offerings (the "ATM Facility"). The Sales Agents are entitled to compensation at a commission equal to 3.0% of the aggregate gross sales price per share sold under the Sales Agreement. Pursuant to the ATM Facility, in 2021, we received aggregate proceeds of $3.3 million, net of commissions and offering expenses from sales of 186,546 shares of our common stock. During the third quarter of 2022, we received proceeds of $8.4 million, net of commissions from the sales of 1,242,132 shares of our common stock. During the fourth quarter of 2022, we received proceeds of $20.1 million, net of commissions from the sales of 2,706,479 shares of our common stock. In January and February 2023, we received aggregate proceeds of $13.4 million, net of commissions from sales of 968,000 shares of our common stock. In February 2023, we entered into Amendment No. 1 to the Sales Agreement with the Sales Agents, pursuant to which we may offer and sell up to $150.0 million shares of our common stock, from time to time, through the ATM Facility.

In July 2022, we completed an underwritten public offering of our common stock, warrants to purchase shares of our common stock and pre-funded warrants to purchase shares of our common stock and raised aggregate proceeds of $88.2 million, net of underwriting discounts and commissions of $5.7 million and other offering costs of $0.6 million. As of December 31, 2022, warrants to purchase 13,107,360 shares of our common stock at an exercise price of $5.325 per share remain outstanding. Our pre-funded warrants to purchase shares of our common stock are exercisable for a nominal amount.

In January 2023, we executed a loan and security agreement (the "2023 Loan Agreement") with the lenders named therein (the "Lenders"). The 2023 Loan Agreement provides up to $100.0 million principal in term loans, consisting of a first tranche of $25.0 million that was funded at closing, two subsequent tranches totaling $25.0 million that may be funded upon the achievement of certain time-based, clinical and regulatory milestones, and a fourth tranche of up to $50.0 million that may be funded upon discretionary approval by the Lenders. Additionally, in January 2023, the first tranche of $25.0 million that was funded at closing pursuant to our 2023 Loan Agreement was primarily used to repay our outstanding obligations under our term loan facility, as amended in May 2021 (the

"2021 Loan Agreement"), including the total principal amount outstanding as of December 31, 2022 of $20.0 million, the total final payment fee of $1.0 million and an early prepayment fee of $0.4 million.

Our primary use of cash is to fund operating expenses, which consist primarily of research and development expenditures related to our lead product candidate, pegozafermin. We plan to increase our research and development expenses for the foreseeable future as we continue the clinical development of our current and future product candidates. At this time, due to the inherently unpredictable nature of clinical development, we cannot reasonably estimate the costs we will incur and the timelines that will be required to complete development, obtain marketing approval, and commercialize our current product candidate or any future product candidates. For the same reasons, we are also unable to predict when, if ever, we will generate revenue from product sales or our current or any future license agreements which we may enter into or whether, or when, if ever, we may achieve profitability. Clinical and preclinical development timelines, the probability of success, and development costs can differ materially from expectations. In addition, we cannot forecast the timing and amounts of milestone, royalty and other revenue from licensing activities, which future product candidates may be subject to future collaborations, when such arrangements will be secured, if at all, and to what degree such arrangements would affect our development plans and capital requirements.

Based on our research and development plans, we expect that our existing cash and cash equivalents and short-term available-for-sale securities as of December 31, 2022, together with the proceeds received in January and February 2023 from our ATM Facility, and proceeds available from the 2023 Loan Agreement, will be sufficient to fund our operations for a period of at least one year from the date this Annual Report on Form 10-K is filed with the SEC. However, our operating plans and other demands on our cash resources may change as a result of many factors, and we may seek additional funds sooner than planned. There can be no assurance that we will be successful in acquiring additional funding at levels sufficient to fund our operations or on terms favorable to us.

Our future funding requirements will depend on many factors, including the following:

- the progress, timing, scope, results and costs of our clinical trials of pegozafermin and preclinical studies or clinical trials of other potential product candidates we may choose to pursue in the future, including the ability to enroll patients in a timely manner for our clinical trials;
- the costs and timing of obtaining clinical and commercial supplies and validating the commercial manufacturing process for pegozafermin and any other product candidates we may identify and develop;
- the cost, timing and outcomes of regulatory approvals;
- the timing and amount of any milestone, royalty or other payments we are required to make pursuant to current or any future collaboration or license agreements;
- costs of acquiring or in-licensing other product candidates and technologies;
- the terms and timing of establishing and maintaining collaborations, licenses and other similar arrangements;
- the costs associated with attracting, hiring and retaining additional qualified personnel as our business grows;
- 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; and
- the cost of preparing, filing, prosecuting, defending and enforcing any patent claims and other intellectual property rights.

We expect to continue to generate substantial operating losses for the foreseeable future as we expand our research and development activities. We will continue to fund our operations primarily through utilization of our current financial resources and through additional raises of capital to advance our current product candidate through clinical development, to develop, acquire or in-license other potential product candidates and to fund operations for the foreseeable future. However, there is no assurance that such funding will be available to us or that it will be obtained on terms favorable to us or will provide us with sufficient funds to meet our objectives. Any failure to raise

capital as and when needed could have a negative impact on our financial condition and on our ability to pursue our business plans and strategies.

To the extent that we raise additional capital through partnerships or licensing arrangements with third parties, we may have to relinquish valuable rights to our product candidates, future revenue streams or research programs or to grant licenses on terms that may not be favorable to us. If we raise additional capital through public or private equity offerings, the ownership interest of our then-existing stockholders will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect our stockholders' rights. If we raise additional capital through debt financing, we may be subject to covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends. If we are unable to obtain adequate financing when needed, we may have to delay, reduce the scope of or suspend one or more of our clinical trials or preclinical studies, research and development programs or 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.

Cash Flows

The following table summarizes our cash flows for the periods presented (in thousands):

	Year Ended December 31,	
	2022	2021
Net cash (used in) provided by		
Operating activities	$ (81,090)	$ (76,781)
Investing activities	(33,943)	7,159
Financing activities	117,831	23,871
Net change in cash and cash equivalents, and restricted cash	$ 2,798	$ (45,751)

Operating Activities

During the year ended December 31, 2022, net cash used in operating activities was $81.1 million, which consisted of a net loss of $102.0 million, partially offset by non-cash charges of $10.4 million and a net change of $10.6 million in our net operating assets and liabilities. The non-cash charges were primarily comprised of $10.4 million in stock-based compensation, $0.8 million in amortization of debt issuance costs and accretion of the final payment fee related to our term loan facility, offset in part by $1.0 million in net accretion of discount on available-for-sale securities. The change in our operating assets and liabilities was primarily due to a $7.4 million increase in accounts payable and accrued expenses and a $3.3 million decrease in prepaid and other current assets due to timing of payments.

During the year ended December 31, 2021, net cash used in operating activities was $76.8 million, which consisted of a net loss of $90.1 million, partially offset by non-cash charges of $10.1 million and a net change of $3.3 million in our net operating assets and liabilities. The non-cash charges were primarily comprised of $8.7 million in stock-based compensation, $0.9 million in amortization of premium on available-for-sale securities and $0.6 million in amortization of debt issuance costs. The change in our operating assets and liabilities was due to a $8.9 million increase in accounts payable and accrued expenses due to the timing of our accounts payable as well as continued expansion of our operations, offset in part by a $5.7 million increase in prepaid and other current assets due to timing of payments.

Investing Activities

During the year ended December 31, 2022, net cash used in investing activities was $33.9 million, which consisted primarily of $152.7 million in purchases of available-for-sale securities, offset by $118.8 million in proceeds from sales and maturities of available-for-sale securities.

During the year ended December 31, 2021, net cash provided by investing activities was $7.2 million, which consisted primarily of $148.4 million in proceeds from sales and maturities of available-for-sale securities, offset by $141.2 million in purchases of available-for-sale securities.

Financing Activities

During the year ended December 31, 2022, net cash provided by financing activities was $117.8 million, which consisted primarily of net proceeds of $88.2 million from the sale of common stock and warrants from our public offering, net proceeds of $28.5 million pursuant to the sale of common stock from our ATM Facility and $1.1 million in net proceeds from the exercise of warrants to purchase our common stock.

During the year ended December 31, 2021, net cash provided by financing activities was $23.9 million, which consisted of $20.0 million in proceeds from our term loan facility, $3.3 million in net proceeds from the sale and issuance of common stock pursuant to our ATM Facility and $0.6 million in proceeds from the issuance of common stock upon exercise of stock options and employee stock purchase plan purchases.

Contractual Obligations and Commitments

Debt Obligations

As of December 31, 2022, our outstanding total principal amount under our 2021 Loan Agreement was $20.0 million. In January 2023, the first tranche of $25.0 million that was funded at closing pursuant to our 2023 Loan Agreement was primarily used to repay the outstanding obligations under our 2021 Loan Agreement, including the total principal amount outstanding of $20.0 million, the total final payment fee of $1.0 million and an early prepayment fee of $0.4 million.

The term loans under our 2023 Loan Agreement mature on January 1, 2027. The maturity date may be extended to July 1, 2027, provided that the second and third tranches are funded, and we achieve certain other financing milestones. The term loans bear interest equal to the greater of (i) 8.45% and (ii) the sum of (a) the Prime Rate as reported in The Wall Street Journal plus (b) 2.25%. Consecutive monthly payments of interest commence in February 2023 and consecutive monthly payments of principal commence in February 2025, or February 2026 provided that certain extension milestones are achieved.

Other Contractual Obligations and Commitments

Our cash requirements greater than one year related to other contractual obligations and commitments include the following:

In April 2018, we entered into two agreements (the “Teva Agreements”) with Teva Pharmaceutical Industries Ltd (“Teva”) under which we acquired certain patents and intellectual property relating to two programs. Pursuant to the Teva Agreements, we could be obligated to pay Teva up to $67.5 million under each program, for a total of $135.0 million, upon the achievement of certain clinical development and commercial milestones. In addition, we are obligated to pay Teva tiered royalties at percentages in the low-to-mid single-digits on worldwide net sales on all products containing the Teva compounds. As of December 31, 2022, the timing and likelihood of achieving the milestones and generating product sales are uncertain.

We lease office space for our corporate headquarters in San Francisco under a lease that expires in January 2025. As of December 31, 2022, undiscounted future minimum lease payments of $0.4 million remain on our lease.

In addition, we enter into agreements in the normal course of business with contract research organizations, contract manufacturing organizations and other vendors for research and development services. Such agreements generally provide for termination upon written notice but obligate us to reimburse vendors for any time or costs incurred through the date of termination.

Critical Accounting Estimates

Our management's discussion and analysis of our financial condition and results of operations is based on our consolidated financial statements, which have been prepared in accordance with United States generally accepted accounting principles. The preparation of these consolidated financial statements requires us to make estimates and assumptions that affect the reported amounts of assets and liabilities and the disclosure of contingent assets and liabilities as of the date of the consolidated financial statements, as well as the reported expenses incurred during the reporting periods. Our estimates are based on our historical experience and on various other factors that we believe are reasonable under the circumstances, the results of which form the basis for making judgments about the carrying value of assets and liabilities that are not readily apparent from other sources. Actual results may differ from these estimates under different assumptions or conditions. We believe that the accounting policies discussed below are critical to understanding our historical and future performance, as these policies relate to the more significant areas involving management's judgments and estimates.

While our significant accounting policies are described in the notes to our consolidated financial statements included elsewhere in this Annual Report on Form 10-K, we believe that the following critical accounting policies are most important to understanding and evaluating our reported financial results.

Accrued Research and Development Expenses

We record accrued expenses for estimated preclinical and clinical trial and research expenses related to the services performed but not yet invoiced pursuant to contracts with research institutions, contract research organizations and clinical manufacturing organizations that conduct and manage preclinical studies, and clinical trials, and research services on our behalf. Payments for these services are based on the terms of individual agreements and payment timing may differ significantly from the period in which the services were performed. Our estimates are based on factors such as the work completed, including patient enrollment levels. We monitor patient enrollment levels and related activity to the extent reasonably possible and make judgments and estimates in determining the accrued balance in each reporting period. Our estimates of accrued expenses are based on the facts and circumstances known at the time. If we underestimate or overestimate the level of services performed or the costs of these services, our actual expenses could differ from our estimates. As actual costs become known, we adjust our accrued expenses. To date, we have not experienced significant changes in our estimates of preclinical studies and clinical trial accruals.

Stock-Based Compensation

We measure compensation related to all equity awards granted to employees, directors, and non-employee service providers, including stock options and restricted stock units based on the estimated fair value. We recognize forfeitures as they occur.

We estimate the fair value of stock option awards on the date of grant, and the resulting stock-based compensation, using the Black-Scholes option-pricing model. The grant date fair value of stock option awards, which have graded vesting, is recognized as an expense using the straight-line method over the requisite service period of each award, which is generally the vesting period of the respective awards.

We use the Black-Scholes option-pricing model to estimate the fair value of stock option awards that requires the use of subjective assumptions to determine the fair value of equity awards. These assumptions include:

- Expected volatility— Since we have limited trading history for our common stock, expected volatility is estimated based on weighting our volatility and the volatility of comparable publicly traded biotechnology companies during the equivalent period of the calculated expected term of the options granted. We chose comparable companies based on their similar size, stage in the life cycle, or area of specialty. There is a degree of uncertainty in determining a comparable peer group as each of the peers are engaged in varied research and development activities, the timing and progress of which differ within the peer group.

- Expected term—The expected term of options granted to employees and directors is determined using the "simplified" method. Under this approach, the expected term is presumed to be the midpoint between the weighted-average vesting term and the contractual term of the option. The simplified method makes the assumption that the employee will exercise stock options evenly over the period when the stock options are vested and ending on the date when the stock options would expire. The expected option term for options granted to non-employees is estimated on a grant-by-grant basis.
- Risk-free interest rate—The risk-free interest rate is based on the U.S. Treasury zero coupon bonds in effect on the grant date for periods with an equivalent expected term as the option.
- Expected dividend—We have never paid dividends and have no foreseeable plans to pay dividends on our shares of common stock. Therefore, we use an expected dividend of zero.

We will continue to use judgment in evaluating the expected volatility and expected term utilized for our stock-based compensation calculations on a prospective basis.

The fair value of restricted stock units is based on the fair value of our common stock on the date of grant. The grant date fair value of restricted stock units with service vesting conditions is recognized over the requisite service period on a straight-line basis. For restricted stock units with performance vesting conditions, we evaluate the probability of achieving the performance condition at each reporting date and recognize expense for such performance awards over the requisite service period using the accelerated attribution method. We recognize forfeitures as they occur.

Recent Accounting Pronouncements

See Note 2 to our consolidated financial statements appearing under Part II, Item 8 for more information about recent accounting pronouncements, the timing of their adoption, and our assessment, to the extent we have made one yet, of their potential impact on our financial condition of results of operations.

JOBS Act Accounting Election

We are an emerging growth company, as defined in the Jumpstart Our Business Startups Act of 2012 (the "JOBS Act"). Under the JOBS Act, emerging growth companies can delay adopting new or revised accounting standards issued subsequent to the enactment of the JOBS Act until such time as those standards apply to private companies.

We have elected to use this 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 we (i) are no longer an emerging growth company or (ii) affirmatively and irrevocably opt out of the extended transition period provided in the JOBS Act. As a result, our consolidated financial statements and our interim consolidated financial statements may not be comparable to companies that comply with new or revised accounting pronouncements.

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

We are a smaller reporting company, as defined by Rule 12b-2 under the Securities and Exchange Act of 1934 and in Item 10(f)(1) of Regulation S-K, and are not required to provide the information under this item.

Item 8. Financial Statements and Supplementary Data.

89BIO, INC.

INDEX TO CONSOLIDATED FINANCIAL STATEMENTS

Report of Independent Registered Public Accounting Firm

To the Stockholders and Board of Directors
89bio, Inc.:

Opinion on the Consolidated Financial Statements

We have audited the accompanying consolidated balance sheets of 89bio, Inc. and subsidiaries (the Company) as of December 31, 2022 and 2021, the related consolidated statements of operations and comprehensive loss, stockholders' equity, and cash flows for each of the years in the two-year period ended December 31, 2022, and the related notes (collectively, the consolidated financial statements). In our opinion, the consolidated financial statements present fairly, in all material respects, the financial position of the Company as of December 31, 2022 and 2021, and the results of its operations and its cash flows for each of the years in the two-year period ended December 31, 2022, in conformity with U.S. generally accepted accounting principles.

Basis for Opinion

These consolidated financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on these consolidated 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 consolidated 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 consolidated 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 consolidated 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 consolidated financial statements. We believe that our audits provide a reasonable basis for our opinion.

/s/ KPMG LLP

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

San Francisco, California
March 14, 2023

89bio, Inc.
Consolidated Balance Sheets
(in thousands, except share and per share amounts)

	As of December 31,	
	2022	2021
Assets		
Current assets:		
Cash and cash equivalents	$ 55,255	$ 52,432
Restricted cash	—	25
Short-term available-for-sale securities	132,905	98,288
Prepaid and other current assets	7,920	11,237
Total current assets	196,080	161,982
Operating lease right-of-use asset	363	—
Property and equipment, net	92	150
Other assets	289	290
Total assets	$ 196,824	$ 162,422
Liabilities and stockholders' equity		
Current liabilities:		
Accounts payable	$ 12,502	$ 6,843
Accrued expenses	11,944	10,194
Operating lease liability, current	168	—
Term loan, current	—	2,500
Total current liabilities	24,614	19,537
Operating lease liability, non-current	186	—
Term loan, non-current, net	19,691	16,898
Other non-current liability	501	30
Total liabilities	44,992	36,465
Commitments and contingencies (Note 5)		
Stockholders' equity:		
Preferred stock, $0.001 par value, 10,000,000 shares authorized as of December 31, 2022 and 2021; no shares issued and outstanding as of December 31, 2022 and 2021	—	—
Common stock, $0.001 par value, 100,000,000 shares authorized as of December 31, 2022 and 2021; 50,560,590 and 20,317,204 shares issued and outstanding as of December 31, 2022 and 2021, respectively	51	20
Additional paid-in capital	467,374	339,218
Accumulated other comprehensive loss	(350)	(64)
Accumulated deficit	(315,243)	(213,217)
Total stockholders' equity	151,832	125,957
Total liabilities and stockholders' equity	$ 196,824	$ 162,422

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

89bio, Inc.
Consolidated Statements of Operations and Comprehensive Loss
(In thousands, except share and per share amounts)

	Year Ended December 31,	
	2022	2021
Operating expenses:		
Research and development	$ 80,796	$ 70,330
General and administrative	21,453	19,413
Total operating expenses	102,249	89,743
Loss from operations	(102,249)	(89,743)
Interest expense	(1,922)	(674)
Interest income and other, net	2,164	148
Net loss before income tax	(102,007)	(90,269)
Income tax (expense) benefit	(19)	147
Net loss	$ (102,026)	$ (90,122)
Other comprehensive (loss) income:		
Unrealized loss on available-for-sale securities	(299)	(71)
Foreign currency translation adjustments	13	17
Total other comprehensive loss	$ (286)	$ (54)
Comprehensive loss	$ (102,312)	$ (90,176)
Net loss per share, basic and diluted	$ (2.93)	$ (4.48)
Weighted-average shares used to compute net loss per share, basic and diluted	34,806,349	20,098,340

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

89bio, Inc.
Consolidated Statements of Stockholders' Equity
(In thousands, except share amounts)

	Common Stock		Additional Paid-in Capital	Accumulated Other Comprehensive Loss	Accumulated Deficit	Total Stockholders' Equity
	Shares	Amounts				
Balance as of December 31, 2020	19,931,660	$ 20	$ 326,046	$ (10)	$ (123,095)	$ 202,961
Issuance of common stock in at-the-market public offerings, net of issuance costs	186,546	—	3,289	—	—	3,289
Issuance of common stock upon exercise of stock options	188,286	—	487	—	—	487
Issuance of common stock upon ESPP purchases	10,712	—	144	—	—	144
Issuance of common stock warrant in connection with term loan facility	—	—	574	—	—	574
Stock-based compensation	—	—	8,678	—	—	8,678
Net loss	—	—	—	—	(90,122)	(90,122)
Other comprehensive loss	—	—	—	(54)	—	(54)
Balance as of December 31, 2021	20,317,204	$ 20	$ 339,218	$ (64)	$ (213,217)	$ 125,957
Issuance of common stock and warrants in public offering, net of issuance costs	18,675,466	20	88,219	—	—	88,239
Issuance of common stock in at-the-market public offering, net of issuance costs	3,948,611	4	28,449	—	—	28,453
Issuance of common stock upon exercise of warrants	4,202,499	4	1,078	—	—	1,082
Issuance of common stock upon cashless exercise of warrants	3,143,682	3	(3)	—	—	—
Issuance of common stock upon exercise of stock options	151,061	—	305	—	—	305
Issuance of common stock upon ESPP purchases	18,364	—	50	—	—	50
Issuance of common stock upon vesting of restricted stock units, net of withholding taxes	103,703	—	(298)	—	—	(298)
Stock-based compensation	—	—	10,356	—	—	10,356
Net loss	—	—	—	—	(102,026)	(102,026)
Other comprehensive loss	—	—	—	(286)	—	(286)
Balance as of December 31, 2022	50,560,590	$ 51	$ 467,374	$ (350)	$ (315,243)	$ 151,832

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

89bio, Inc.
Consolidated Statements of Cash Flows
(In thousands)

	Year Ended December 31,	
	2022	2021
Cash flows from operating activities:		
Net loss	$ (102,026)	$ (90,122)
Adjustments to reconcile net loss to net cash used in operating activities:		
Stock-based compensation	10,356	8,678
Net (accretion) amortization on available-for-sale securities	(980)	865
Amortization of debt issuance costs and accretion of final payment fee	764	617
Non-cash operating lease expense	175	—
Depreciation	65	79
Deferred tax assets	—	(150)
Changes in operating assets and liabilities:		
Prepaid and other current assets	3,331	(5,672)
Accounts payable	5,659	4,778
Accrued expenses	1,750	4,146
Operating lease liability	(184)	—
Net cash used in operating activities	(81,090)	(76,781)
Cash flows from investing activities:		
Proceeds from sales and maturities of available-for-sale securities	118,760	148,422
Purchases of available-for-sale securities	(152,696)	(141,200)
Purchases of property and equipment	(7)	(63)
Net cash (used in) provided by investing activities	(33,943)	7,159
Cash flows from financing activities:		
Proceeds from issuance of common stock and warrants in public offering, net of issuance costs	88,239	—
Proceeds from issuance of common stock in at-the-market public offering, net of issuance costs	28,453	3,289
Proceeds from issuance of common stock upon exercise of warrants	1,082	—
Proceeds from issuance of common stock upon exercise of stock options	305	487
Proceeds from issuance of common stock upon ESPP purchases	50	144
Payment of withholding taxes related to restricted stock units	(298)	—
Proceeds from term loan facility, net of issuance costs	—	19,951
Net cash provided by financing activities	117,831	23,871
Net change in cash and cash equivalents, and restricted cash	2,798	(45,751)
Cash and cash equivalents, and restricted cash at beginning of period	52,457	98,208
Cash and cash equivalents, and restricted cash at end of period	$ 55,255	$ 52,457
Components of cash and cash equivalents, and restricted cash:		
Cash and cash equivalents	$ 55,255	$ 52,432
Restricted cash	—	25
Total cash and cash equivalents, and restricted cash	$ 55,255	$ 52,457
Supplemental disclosures of cash information:		
Cash paid for interest	$ 1,076	$ 16
Cash paid for operating leases	$ 234	$ —
Supplemental disclosures of noncash information:		
Remeasurement of lease liability and right of use asset in connection with lease modification	$ 338	$ —
Issuance of common stock warrant in connection with term loan facility	$ —	$ 574

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

1. Organization and Basis of Presentation

Description of Business

89bio, Inc. ("89bio" or the "Company") is a clinical-stage biopharmaceutical company focused on the development and commercialization of innovative therapies for the treatment of liver and cardio-metabolic diseases. The Company's lead product candidate, pegozafermin (previously BIO89-100), a specifically engineered glycoPEGylated analog of fibroblast growth factor 21, is currently being developed for the treatment of nonalcoholic steatohepatitis and for the treatment of severe hypertriglyceridemia.

89bio, Inc. was formed as a Delaware corporation in June 2019 to carry on the business of 89Bio Ltd., which was incorporated in Israel in January 2018.

Liquidity

The accompanying consolidated financial statements have been prepared assuming the Company will continue as a going concern, which contemplates the realization of assets and liquidation of liabilities in the normal course of business. To date, the Company has not generated revenues from its activities and has incurred substantial operating losses. Management expects the Company to continue to generate substantial operating losses for the foreseeable future until it completes development of its products and seeks regulatory approvals to market such products. The Company had cash and cash equivalents and short-term available-for-sale securities of $188.2 million as of December 31, 2022.

The Company expects that its cash and cash equivalents and short-term available-for-sale securities as of December 31, 2022, together with proceeds received in January and February 2023 from its ATM Facility (see Note 7 and Note 11), and proceeds available from the 2023 Loan Agreement (see Note 6 and Note 11), will be sufficient to fund operating expenses and capital expenditure requirements for a period of at least one year from the date these audited consolidated financial statements are filed with the Securities and Exchange Commission.

2. Summary of Significant Accounting Policies

Basis of Presentation

The consolidated financial statements have been prepared in conformity with accounting principles generally accepted in the United States ("U.S. GAAP").

Reclassification

Certain prior year amounts in the Company's consolidated statements of operations and comprehensive loss have been reclassified to conform to the current year presentation. Specifically, interest expense is disclosed separately on the Company's consolidated statements of operations and comprehensive loss, which had no impact on reported net loss, comprehensive loss, or loss per share.

Principles of Consolidation

The accompanying consolidated financial statements include the accounts of the Company and its wholly owned subsidiaries. All intercompany balances and transactions have been eliminated in consolidation.

Use of Estimates

The preparation of consolidated financial statements in conformity with U.S. GAAP requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities and disclosure of contingent assets and liabilities as of the date of the consolidated financial statements and the reported amounts of expenses during the reporting period. Significant estimates and assumptions made in the accompanying consolidated financial statements include but are not limited to accrued research and development expenses and to the fair value of stock options. The Company evaluates its estimates and assumptions on an ongoing basis using historical experience and other factors and adjusts those estimates and assumptions when facts and circumstances dictate. Actual results could differ from those estimates.

Foreign Currencies

Certain transactions during the year ended December 31, 2022 and 2021 were denominated in currencies other than the U.S. dollar. Gains and losses from foreign currency transactions were not material for all periods presented and are reflected in the consolidated statements of operations and comprehensive loss as a component of interest income and other, net. The Company's subsidiary in Lithuania uses the Euro as its functional currency for financial reporting. The re-measurement from Euros to U.S. dollars results in translation gain and loss adjustments, which are reflected as a component of comprehensive loss as foreign currency translation adjustments.

Fair Value Measurements

Financial assets and liabilities are recorded at fair value on a recurring basis in the consolidated balance sheets. The carrying values of Company's financial assets and liabilities, including cash and cash equivalents, restricted cash, prepaid and other current assets, accounts payable, and accrued expenses approximate to their fair value due to the short-term nature of these instruments. The fair value of the Company's term loan approximates its carrying value, or amortized cost, due to the prevailing market rates of interest rates it bears. Fair value is defined as the price that would be received to sell an asset or paid to transfer a liability (an exit price) in an orderly transaction between market participants at the reporting date. Assets and liabilities recorded at fair value are categorized based upon the level of judgment associated with the inputs used to measure their fair value. Hierarchical levels are directly related to the amount of subjectivity with the inputs to the valuation of these assets or liabilities as follows:

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

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

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

Concentrations of Credit Risk

Financial instruments that potentially subject the Company to a concentration of credit risk consist primarily of cash and cash equivalents and short-term available-for-sale securities. Bank deposits are held by accredited financial institutions and these deposits may at times be in excess of insured limits. The Company limits its credit risk associated with cash and cash equivalents by placing them with financial institutions that it believes are of high quality. The Company has not experienced any losses on its deposits of cash or cash equivalents. The Company limits amounts invested in available-for-sale securities by credit rating, maturity, industry group, investment type and issuer, except for securities issued by the U.S. government. The Company is not exposed to any significant concentrations of credit risk from these financial instruments.

Other Risks and Uncertainties

The Company's future results of operations involve a number of other risks and uncertainties. Factors that could affect the Company's future operating results and cause actual results to vary materially from expectations include, but are not limited to, the Company's early stages of clinical drug development; the Company's ability to advance product candidates into, and successfully complete, clinical trials on the timelines it projects; the Company's ability to adequately demonstrate sufficient safety and efficacy of its product candidates; the Company's ability to enroll patients in its ongoing and future clinical trials; the Company's ability to successfully manufacture and supply its product candidates for clinical trials; the Company's ability to obtain additional capital to finance its operations; uncertainties related to the projections of the size of patient populations suffering from the diseases the Company is targeting; the Company's ability to obtain, maintain, and protect its intellectual property rights; developments relating to the Company's competitors and its industry, including competing product candidates and therapies; general economic and market conditions; and other risks and uncertainties.

The Company's product candidates will require approvals from the U.S. Food and Drug Administration and comparable foreign regulatory agencies prior to commercial sales in their respective jurisdictions. There can be no assurance that any product candidates will receive the necessary approvals. If the Company is denied approval, approval is delayed or the Company is unable to maintain approval for any product candidate, it could have a materially adverse impact on the Company.

The ongoing COVID-19 pandemic has disrupted and may continue to disrupt the Company's business and delay its preclinical and clinical programs and timelines. The extent to which the COVID-19 pandemic may impact the Company's future operating results and financial condition is uncertain.

Segment Reporting

The Company has one operating segment. The Company's chief operating decision maker, its Chief Executive Officer, manages the Company's operations on a consolidated basis for the purposes of allocating resources and evaluating financial performance.

Cash and Cash Equivalents

The Company considers all highly liquid investments purchased with original maturities of three months or less from the purchase date to be cash equivalents. Cash equivalents consist primarily of amounts invested in money market funds and commercial paper that are stated at fair value.

Investments

Investments have been classified as available-for-sale and are carried at estimated fair value as determined based upon quoted market prices or pricing models for similar securities. Management determines the appropriate classification of its available-for-sale investments in debt securities at the time of purchase. Generally, investments with original maturities beyond three months at the date of purchase are classified as short-term because it is management's intent to use the investments to fund current operations or to make them available for current operations.

Unrealized gains and losses are excluded from net loss and are reported as a component of comprehensive loss. The Company periodically evaluates whether declines in fair values of its available-for-sale securities below their book value are other-than-temporary. This evaluation consists of several qualitative and quantitative factors regarding the severity and duration of the unrealized loss as well as the Company's ability and intent to hold the available-for-sale security until a forecasted recovery occurs. Additionally, the Company assesses whether it has plans to sell the security or it is more likely than not it will be required to sell any available-for-sale securities before recovery of its amortized cost basis. Realized gains and losses and declines in fair value judged to be other than temporary, if any, on available-for-sale securities are included in interest income and other, net. The cost of investments sold is based on the specific-identification method. The Company has not experienced any material realized gains or losses or other-than-temporary losses in the periods presented.

Leases

The Company is a lessee in noncancellable operating leases for office space. Beginning in 2022, the Company accounts for leases in accordance with Accounting Standards Update ("ASU") 2016-02, *Leases* (*Topic 842*). The Company determines if an arrangement is a lease or contains an embedded lease at inception. The Company accounts for a contract as a lease when it has the right to control the asset for a period of time while obtaining substantially all of the asset's economic benefits. For arrangements that meet the definition of a lease, the Company determines the initial classification and measurement of its right-of-use ("ROU") asset and lease liability at the lease commencement date and thereafter if modified. Operating lease ROU assets represent the Company's right to use an underlying asset for the lease term and lease liabilities represent the Company's obligation to make the contractual lease payments over the lease term. The ROU asset is initially measured at cost, which comprises the initial amount of the lease liability adjusted for lease payments made at or before the lease commencement date, plus any initial direct costs incurred less any lease incentives received. The operating lease liability is initially measured at the present value of the unpaid lease payments at the lease commencement date. The lease liability is subsequently measured at amortized cost using the effective-interest method. The lease term includes any renewal options that the Company is reasonably assured to exercise. The present value of lease payments is determined by using the interest rate implicit in the lease, if that rate is readily determinable, otherwise, the Company uses its estimated collateralized incremental borrowing rate for the lease term. The Company has elected not to record leases with an original term of twelve months or less on its consolidated balance sheets and recognizes those lease payments in operating expenses in the consolidated statements of operations and comprehensive loss. The Company's short-term lease is not material.

In addition, the Company's leases may require it to pay additional costs, such as utilities, maintenance, and other operating costs, which are generally referred to as non-lease components and vary based on future outcomes. The Company has elected to not separate lease and non-lease components. Only the fixed costs for lease components and their associated non-lease components are accounted for as a single lease component and recognized as part of a ROU asset and lease liability. Any variable expenses are recognized in operating expenses as incurred. Rent expense for an operating lease liability is recognized on a straight-line basis over the lease term and is included in operating expenses in the consolidated statements of operations and comprehensive loss.

Property and Equipment, Net

Property and equipment are stated at cost, less accumulated depreciation. Depreciation is calculated on a straight-line basis over the estimated useful lives of the related assets, generally ranging from three to seven years. Leasehold improvements are amortized on a straight-line basis over the shorter of the assets' estimated useful life or the remaining term of the lease. Upon retirement or sale of the assets, the cost and related accumulated depreciation and amortization are removed from the consolidated balance sheets and the resulting gains or losses are recorded in the consolidated statements of operations and comprehensive loss. Maintenance and repair costs are expensed as incurred.

Impairment of Long-Lived Assets

The Company periodically evaluates its long-lived assets, including property and equipment, for impairment whenever events or changes in business circumstances indicate that the carrying amount of the assets or group of assets may not be fully recoverable. If indicators of impairment exist and the undiscounted future cash flows that the assets are expected to generate are less than the carrying value of the assets, then the Company will reduce the carrying amount of the assets through an impairment charge, to their estimated fair values based on a discounted cash flow approach or, when available and appropriate, to comparable market values. There were no such indicators for the periods presented.

Accrued Research and Development Expenses

The Company estimates preclinical and clinical study and research expenses based on the services performed, pursuant to contracts with research institutions that conduct and manage preclinical and clinical studies and research services on its behalf. The Company records the costs of research and development activities based upon the estimated services provided but not yet invoiced and includes these costs in accrued expenses in the consolidated balance sheets. These costs are a component of the Company's research and development expenses.

The Company accrues for these costs based on factors such as estimates of the work completed in accordance with agreements established with its third-party service providers. The Company makes judgments and estimates in determining the accrued expenses balance. As actual costs become known, the Company adjusts its accrued expenses. The Company has not experienced any material differences between accrued costs and actual costs incurred. However, the status and timing of actual services performed may vary from the Company's estimates, resulting in adjustments to expense in future periods. Changes in these estimates that result in material changes to the Company's accrued expenses could materially affect the Company's results of operations. Contingent milestone payments, if any, are expensed when the milestone results are probable and estimable, which is generally upon achievement of the milestone.

Warrants to Purchase Common Stock

The Company classifies warrants indexed to its common stock and meeting the requirements for equity classification within stockholders' equity. This assessment is conducted at the time of warrant issuance and as of each reporting period that the warrants remain outstanding.

Research and Development Expenses

Research and development expenses consist primarily of costs incurred for the development of the Company's lead product candidate, pegozafermin. Research and development expenses consist primarily of external costs related to preclinical and clinical development and related supplies and personnel costs. Personnel costs consist of salaries, employee benefits and stock-based compensation for individuals involved in research and development efforts. Payments associated with agreements to acquire licenses to develop, use, manufacture and commercialize products and purchases of pegozafermin from contract manufacturing organizations that have not reached technological feasibility and do not have alternate future commercial use are expensed as incurred.

Stock-Based Compensation

The Company provides equity awards in the form of stock options and restricted stock units. The Company measures its equity awards made to employees, directors, and non-employee service providers based on estimated fair values and recognizes stock-based compensation over the requisite service period. The Company accounts for forfeitures as they occur.

The Company estimates the fair value of stock option awards on the date of grant using a Black-Scholes option pricing model. The Company recognizes compensation for the value of stock options awards, which have graded vesting, using the straight-line method over the requisite service period of each award.

The Black-Scholes option pricing model requires a number of assumptions, of which the most significant are expected volatility, expected option term (the time from the grant date until the options are exercised or expire), risk-free rate, and expected dividend rate. These assumptions include:

- Expected volatility—Since the Company has limited trading history for its common stock, expected volatility is estimated based on weighting the Company's volatility and the volatility of comparable publicly traded biotechnology companies during the equivalent period of the calculated expected term of the options granted. The comparable companies were chosen based on their similar size, stage in the life cycle, or area of specialty. There is a degree of uncertainty in determining a comparable peer group as each of the peers are engaged in varied research and development activities, the timing and progress of which differ within the peer group.
- Expected term—The expected term of options granted to employees and directors is determined using the "simplified" method. Under this approach, the expected term is presumed to be the midpoint between the weighted-average vesting term and the contractual term of the option. The simplified method makes the assumption that the employee will exercise stock options evenly over the period when the stock options are vested and ending on the date when the stock options would expire. The expected option term for options granted to non-employees is estimated on a grant-by-grant basis.
- Risk-free interest rate—The risk-free interest rate is based on the U.S. Treasury zero coupon bonds in effect on the grant date for periods with an equivalent expected term as the option.
- Expected dividend—The Company has never paid dividends and has no foreseeable plans to pay dividends on its shares of common stock. Therefore, an expected dividend of zero is used.

The fair value of restricted stock units is based on the fair value of the Company's common stock on the date of grant. The grant date fair value of restricted stock units with service vesting conditions is recognized over the requisite service period on a straight-line basis. For restricted stock units with performance vesting conditions, the Company evaluates the probability of achieving the performance condition at each reporting date and recognizes expense for such performance awards over the requisite service period using the accelerated attribution method.

Income Taxes

Income taxes are accounted for under the asset and liability method. Under this method, deferred tax assets and liabilities are recognized for the future tax consequences attributable to differences between the consolidated financial statements carrying amounts of existing assets and liabilities and their respective tax bases and operating loss and tax credit carryforwards. Deferred tax assets and liabilities are measured using enacted tax rates applied to taxable income in the years in which those temporary differences are expected to be realized. The effect on deferred tax assets and liabilities of a change in tax rates is recognized as income or loss in the period that includes the enactment date. A valuation allowance is established when necessary to reduce deferred tax assets to the amount expected to be realized. Interest and penalties related to unrecognized tax benefits are included within the provision of income tax.

Basic and Diluted Net Loss per Share

Basic loss per share is computed by dividing net loss by the weighted-average number of shares of common stock outstanding during the period. Diluted loss per share is computed by dividing net loss by the weighted-average number of shares of common stock outstanding together with the number of additional shares of common stock that would have been outstanding if all potentially dilutive shares of common stock had been issued. Since the Company is in a loss position for the periods presented, basic net loss per share is the same as diluted net loss per share since the effects of potentially dilutive securities are antidilutive. Shares of the Company's common stock underlying pre-funded warrants exercisable for nominal consideration are included in the computation of basic and diluted net loss per share, even if antidilutive.

Comprehensive Loss

The Company's comprehensive loss is comprised of net loss and changes in unrealized gains or losses on available-for-sale securities and foreign currency translation adjustments.

Recently Adopted Accounting Standards

In February 2016, the Financial Accounting Standards Board ("FASB") issued ASU 2016-02, *Leases* (*Topic 842*), or Accounting Standards Codification ("ASC") 842, which requires lessees to recognize leases on the balance sheet and disclose key information about leasing arrangements. ASC 842 establishes a ROU model that requires a lessee to recognize a ROU asset and lease liability on the balance sheet for all leases with a term longer than 12 months. Leases are classified as finance or operating, with classification affecting the pattern and classification of expense recognition in the income statement.

On January 1, 2022, the Company adopted ASC 842 using the modified retrospective transition method and elected the practical expedients to not reassess whether any expired or existing contracts are or contain leases, carry forward its historical lease classification and not reassess initial direct costs for existing leases. Upon adoption of ASC 842, the Company recorded an operating ROU asset of $0.2 million and an operating lease liability of $0.2 million on its consolidated balance sheet. There was no adjustment to the opening balance of accumulated deficit as a result of adoption. Results for the year ended December 31, 2022 are presented under ASC 842. Prior period amounts preceding January 1, 2022 continue to be reported in accordance with the Company's historical accounting under the previous lease guidance, ASC 840.

Recent Accounting Pronouncements

In June 2016, the FASB issued ASU 2016-13, *Financial Instruments—Credit Losses (Topic 326)*: *Measurement of Credit Losses on Financial Instruments* ("ASU 2016-13"), which replaces the existing incurred loss impairment model with an expected credit loss model and requires a financial asset measured at amortized cost to be presented at the net amount expected to be collected. As an emerging growth company, ASU 2016-13 is effective for the Company for the year ending December 31, 2023 and interim periods within that fiscal year and must be adopted using a modified retrospective approach, with certain exceptions. The Company is evaluating the impact of this standard and does not expect the adoption of ASU 2016-13 to have a material impact on the Company's consolidated financial statements and related disclosures.

3. Fair Value Measurements

The following table presents the Company's financial assets measured at fair value on a recurring basis by level within the fair value hierarchy as of December 31, 2022 (in thousands):

	Valuation Hierarchy	Amortized Cost	Unrealized Gains	Unrealized Losses	Fair Value
Money market funds	Level 1	$ 18,224	$ —	$ —	$ 18,224
Commercial paper	Level 2	104,279	1	(84)	104,196
U.S. government bonds	Level 2	18,225	1	(109)	18,117
Agency bonds	Level 2	13,986	—	(78)	13,908
Corporate debt securities	Level 2	10,488	—	(62)	10,426
U.S. treasury bills	Level 2	7,414	1	(21)	7,394
Agency discount securities	Level 2	5,216	9	—	5,225
Non-U.S. debt securities	Level 2	3,975	—	(20)	3,955
Total cash equivalents and available-for-sale securities		$ 181,807	$ 12	$ (374)	$ 181,445
Classified as:					
Cash equivalents					$ 48,540
Short-term available-for-sale securities					132,905
Total cash equivalents and available-for-sale securities					$ 181,445

The following table summarizes the Company's cash equivalents and available-for-sale securities by contractual maturity as of December 31, 2022 (in thousands):

Within one year	$ 175,243
After one year through two years	6,202
Total cash equivalents and available-for-sale securities	$ 181,445

The following table presents the Company's financial assets measured at fair value on a recurring basis by level within the fair value hierarchy as of December 31, 2021 (in thousands):

	Valuation Hierarchy	Amortized Cost	Unrealized Gains	Unrealized Losses	Fair Value
Money market funds	Level 1	$ 21,477	$ —	$ —	$ 21,477
Commercial paper	Level 2	59,647	—	(10)	59,637
U.S. government bonds	Level 2	21,662	—	(42)	21,620
Corporate debt securities	Level 2	8,776	1	(1)	8,776
Agency bonds	Level 2	7,747	1	(7)	7,741
Municipal bonds	Level 2	4,251	—	(4)	4,247
Non-U.S. debt securities	Level 2	2,506	—	(1)	2,505
Total cash equivalents and available-for-sale securities		$ 126,066	$ 2	$ (65)	$ 126,003
Classified as:					
Cash equivalents					$ 27,715
Short-term available-for-sale securities					98,288
Total cash equivalents and available-for-sale securities					$ 126,003

The following table summarizes the Company's cash equivalents and available-for-sale securities by contractual maturity as of December 31, 2021 (in thousands):

Within one year	$ 120,726
After one year through two years	5,277
Total cash equivalents and available-for-sale securities	$ 126,003

4. Consolidated Balance Sheet Components

Prepaid and other current assets consist of the following as of the periods presented (in thousands):

	As of December 31, 2022	As of December 31, 2021
Prepaid research and development	$ 5,727	$ 7,895
Prepaid taxes	646	836
Prepaid other	1,547	2,506
Total prepaid and other current assets	$ 7,920	$ 11,237

Accrued expenses consist of the following as of the periods presented (in thousands):

	As of December 31,	
	2022	2021
Accrued research and development expenses	$ 6,499	$ 6,195
Accrued employee and related expenses	4,165	3,168
Accrued professional and legal fees	1,052	495
Accrued other expenses	228	336
Total accrued expenses	$ 11,944	$ 10,194

5. Commitments and Contingencies

Leases

On January 1, 2022, the Company adopted ASC 842 (see Note 2), and the following disclosures as of and for the year ended December 31, 2022 are presented under ASC 842, while prior period amounts have not been adjusted and continue to be reported in accordance with the historical accounting under ASC 840. Upon adoption, the Company recorded an operating lease ROU asset and lease liability for its lease in San Francisco, which was due to expire in January 2023. Effective August 31, 2022, the Company amended the lease to extend the expiration date of the lease to January 2025, with one option to renew for an additional year that is not reasonably certain to be exercised. The amendment resulted in the remeasurement of the lease liability and ROU asset as of the modification date to reflect the extended term and the Company recorded an incremental ROU asset and lease liability of $0.3 million.

For the year ended December 31, 2022, the Company incurred $0.2 million in rent expense. For the year ended December 31, 2022, variable lease payments and short-term lease costs were immaterial. As of December 31, 2022, the remaining lease term was 2.0 years and the Company's incremental borrowing rate used to determine the operating lease liability was 6.5%.

As of December 31, 2022, the undiscounted future minimum lease payments due under the Company's non-cancellable operating lease are as follows (in thousands):

2023	$ 185
2024	185
2025	7
Total undiscounted future minimum lease payments	$ 377
Less: imputed interest	(23)
Present value of operating lease liability	$ 354

In accordance with ASC 840, rent expense for the year ended December 31, 2021 was $0.3 million. The total future minimum annual payments for operating leases in effect as of December 31, 2021 were as follows (in thousands):

2022	$ 212
2023	7
Total future minimum annual payments	$ 219

Asset Transfer and License Agreement with Teva Pharmaceutical Industries Ltd

In April 2018, the Company concurrently entered into two Asset Transfer and License Agreements (the "Teva Agreements") with Teva Pharmaceutical Industries Ltd ("Teva") under which it acquired certain patents and intellectual property relating to two programs: (1) Teva's glycoPEGylated FGF21 fibroblast growth factor 21 ("FGF21") program, including the compound TEV-47948 (pegozafermin), a glycoPEGylated long-acting FGF21 and (2) Teva's development program of small molecule inhibitors of fatty acid synthase. Pursuant to the Teva Agreements, the Company paid Teva an initial nonrefundable upfront payment of $6.0 million and the Company

could be obligated to pay Teva up to $67.5 million under each program, for a total of $135.0 million, upon the achievement of certain clinical development and commercial milestones. In addition, the Company is obligated to pay Teva tiered royalties at percentages in the low-to-mid single-digits on worldwide net sales on all products containing the Teva compounds.

The Teva Agreements can be terminated (i) by the Company without cause upon 120 days' written notice to Teva, (ii) by either party, if the other party materially breaches any of its obligations under the Teva Agreements and fails to cure such breach within 60 days after receiving notice thereof, or (iii) by either party, if a bankruptcy petition is filed against the other party and is not dismissed within 60 days. In addition, Teva can also terminate the agreement related to the Company's glycoPEGylated FGF21 program in the event the Company, or any of its affiliates or sublicensees, challenges any of the Teva patents licensed to the Company, and the challenge is not withdrawn within 30 days of written notice from Teva.

During the year ended December 31, 2022 and 2021, none of the development and commercial milestones were met and accordingly, there were no milestone payments related to the Teva Agreements.

6. Term Loan

Loan and Security Agreement

In April 2020, the Company entered into a Loan and Security Agreement, (the "Loan Agreement") with the lenders referred to therein, and Silicon Valley Bank ("SVB"), as collateral agent. The Loan Agreement provided for (i) a secured term A loan facility (the "Term A Loan Facility") of up to $10.0 million and (ii) a secured term B loan facility (the "Term B Loan Facility") of up to $5.0 million that became available upon the satisfaction of certain milestones, each of which was available to be drawn through May 31, 2021. The term loan is secured by certain assets of the Borrowers (as defined in the Loan Agreement), including substantially all of the assets of the Company, excluding the Company's intellectual property. The term loan contains customary representations, warranties, affirmative covenants and also certain restrictive covenants.

In April 2020, in connection with the execution of the Loan Agreement, the Company issued SVB a warrant to purchase 25,000 shares of the Company's common stock with a warrant exercise price of $22.06 per share that is immediately exercisable and expires on June 30, 2025, as amended. The fair value of the warrant at the issuance date was determined by using the Black-Scholes option-pricing model and the fair value allocated to the warrant of $0.6 million met the requirements for equity classification within additional paid-in capital. Additionally, the Company incurred $0.2 million in closing costs, which together with the value of the warrants, were recorded as debt issuance costs.

In May 2021, the parties further amended the Loan Agreement (as amended, the "2021 Loan Agreement"). The 2021 Loan Agreement increased the Term A Loan Facility to up to $20.0 million, which was fully drawn as of December 2021. The Term B Loan Facility of up to $5.0 million was available to be drawn upon on achievement of certain additional milestones, on or before September 30, 2022, which expired unused. The 2021 Loan Agreement provided for interest-only payments until October 1, 2022, which could be extended to April 1, 2023, if on or before September 30, 2022, the Company received net cash proceeds of at least $75.0 million from the sale of its equity securities. In July 2022, the Company met the net cash proceeds requirement (see Note 7) and on September 1, 2022, the interest-only period was extended to April 1, 2023. Consecutive monthly payments of principal and interest commence on April 1, 2023 and continue through September 1, 2024, the maturity date of the term loan. The term loan bears interest at the greater of (i) 4.25% and (ii) the sum of (a) the Prime Rate as reported in The Wall Street Journal plus (b) 1.00%. The interest rate on the term loan was 4.25% at inception and 8.50% as of December 31, 2022. In addition, a final payment fee of 5.0% of the principal amount of the loan is due when the term loan becomes due or upon prepayment of the term loan. If the Company elects to prepay the loan, there is also a prepayment fee of between 1.0% and 3.0% of the principal amount of the term loan depending on the timing of prepayment.

In May 2021, in connection with the execution of the 2021 Loan Agreement, the Company issued SVB a warrant to purchase 33,923 shares of the Company's common stock with a warrant exercise price of $19.12 per share that is immediately exercisable and expires on May 28, 2031. The Company determined the fair value of the

warrant at the issuance date by using the Black-Scholes option-pricing model with the following assumptions: risk-free interest rate of 1.6%, no dividends, expected volatility of 98.6% and expected term of 10.0 years. Upon issuance, the fair value of the warrant of $0.6 million was recorded as a debt issuance cost and met the requirements for equity classification within additional paid-in capital in the consolidated balance sheets. In addition, closing costs incurred were not material. In connection with Term B Loan Facility, if funded, the Company was to issue an additional warrant to purchase 11,305 shares of the Company's common stock with the exercise price at the Company's stock price at the time of issuance. However, the Term Loan B Facility expired unused and therefore no additional warrant was issued.

The 2021 Loan Agreement was accounted for as a modification to a credit facility. The related debt issuance costs incurred in May 2021, including the fair value of the warrant, together with the remaining unamortized debt issuance costs related to the Loan Agreement of $0.4 million were recorded as deferred assets and recognized on a straight-line basis as interest expense over the availability of the draw period. As of December 31, 2021, all amounts were drawn under the Term Loan A Facility such that all debt issuance costs were recorded as a debt discount. The carrying value of the debt discount, together with the final payment fee, are recognized using the effective interest method.

In September 2022, the parties agreed the extension of the interest-only period was met as a result of the July 2022 public offering (see Note 7), which was accounted for as a debt modification. A new effective interest rate equating to the revised cash flows of the carrying amount of the original debt was applied prospectively. The Company did not incur any costs in relation to the extension.

In January 2023, the Company executed a loan and security agreement with new lenders (the "2023 Loan Agreement") and repaid its outstanding obligations under the 2021 Loan Agreement (see Note 11). As the Company had the intent and ability to refinance amounts due under the 2021 Loan Agreement pursuant to the terms of the 2023 Loan Agreement, as of December 31, 2022, the current portion of the outstanding principal obligation under the 2021 Loan Agreement was classified as long-term. As of December 31, 2022, the Company's total obligations under the 2021 Loan Agreement were $19.7 million classified as term loan, non-current, net and $0.5 million classified as other non-current liability related to the final payment fee. The term loan, non-current, net is comprised of the outstanding principal amount of $20.0 million net of $0.3 million of unamortized debt discount.

7. Stockholders' Equity

As of December 31, 2022, the Company's shares of common stock available for future issuance were as follows:

Shares available for future grant under the equity incentive plan	241,635
Shares available for future issuance under the employee stock purchase plan	729,218
Shares available for future issuance upon the exercise of warrants and pre-funded warrants	13,966,283
Total available for future issuance	14,937,136

Public Offerings

At-the-Market Offerings

In March 2021, the Company entered into a sales agreement (as amended, the "Sales Agreement") with SVB Securities LLC and Cantor Fitzgerald & Co. (the "Sales Agents") pursuant to which the Company may offer and sell up to $75.0 million of shares of its common stock, from time to time, in "at-the-market" offerings (the "ATM Facility"). The Sales Agents are entitled to compensation at a commission equal to 3.0% of the aggregate gross sales price per share sold under the Sales Agreement. Pursuant to the ATM Facility, in 2021, the Company received aggregate proceeds of $3.3 million, net of commissions and offering expenses from sales of 186,546 shares of its common stock and, in 2022, received aggregate proceeds of $28.5 million, net of commissions from the sales of 3,948,611 shares of its common stock.

July 2022 Public Offering

In July 2022, the Company completed an underwritten public offering of its common stock, warrants to purchase shares of its common stock and pre-funded warrants to purchase shares of its common stock. The Company sold 18,675,466 shares of its common stock with accompanying warrants to purchase up to 9,337,733 shares of its common stock at a combined public offering price of $3.55 per share. The Company also sold 7,944,252 pre-funded warrants to purchase shares of its common stock with accompanying warrants to purchase up to 3,972,126 shares of its common stock at a combined public offering price of $3.549 per pre-funded warrant, which represents the per share public offering price for the common stock less $0.001 per share, the exercise price for each pre-funded warrant. The Company raised net proceeds of $88.2 million, after deducting underwriting discounts and commissions of $5.7 million and other offering costs of $0.6 million.

The exercise of the outstanding warrants is subject to a beneficial ownership limitation of 9.99%, or at the election of the holder prior to the issuance of the warrant, 4.99%. The exercise of the outstanding pre-funded warrants is subject to a beneficial ownership limitation of 9.99%, or at the election of the holder prior to the issuance of the pre-funded warrant, 4.99%, which a holder may increase or decrease from time to time but shall not exceed 19.99%. The exercise price and number of shares of common stock issuable upon the exercise of the warrants and pre-funded warrants are subject to adjustment in the event of any stock dividends, stock splits, reverse stock split, recapitalization, or reorganization or similar transaction, as described in the agreements. Under certain circumstances, the warrants and pre-funded warrants may be exercisable on a “cashless” basis. The warrants and pre-funded warrants were classified as a component of stockholders’ equity and additional paid-in capital because such warrants and pre-funded warrants (i) are freestanding financial instruments that are legally detachable and separately exercisable from the equity instruments, (ii) are immediately exercisable, (iii) do not embody an obligation for the Company to repurchase its shares, (iv) permit the holders to receive a fixed number of common shares upon exercise, (v) are indexed to the Company’s common stock and (vi) meet the equity classification criteria. In addition, the warrants and pre-funded warrants do not provide any guarantee of value or return.

Common Stock Warrants

As of December 31, 2022, the Company’s outstanding warrants to purchase shares of its common stock were as follows:

	Shares of Common Stock Underlying Warrants	Exercise Price Per Share	Expiration Date
Warrant issued with term loan	25,000	$ 22.06	June 30, 2025
Warrant issued with term loan	33,923	$ 19.12	May 28, 2031
Warrants issued in public offering	13,107,360	$ 5.325	July 1, 2024
Pre-funded warrants issued in public offering	800,000	$ 0.001	Do not expire
Total outstanding	13,966,283		

8. Stock-Based Compensation

Equity Incentive Plan

In September 2019, the Company’s board of directors adopted the 2019 Equity Incentive Plan (the “2019 Plan”), which also became effective in September 2019. The Company initially reserved 2,844,193 shares of common stock for issuance under the 2019 Plan. In addition, the number of shares of common stock reserved for issuance under the 2019 Plan will automatically increase on the first day of January for a period of up to ten years in an amount equal to 4% of the total number of shares of the Company’s capital stock outstanding on the immediately preceding December 31, or a lesser number of shares determined by the Company’s board of directors.

The board of directors determines the period over which options become exercisable and options generally vest over a four-year period, with 25% of options vesting on the first anniversary of employment, and thereafter, the remaining options vesting quarterly, over the following 36-month period. The options expire within ten years from

the date of grant. The exercise price of awards granted will not be less than the estimated fair value of the shares on the date of grant. The 2019 Plan also permits the board of directors to grant restricted stock units, which are subject to continued service conditions.

Employee Stock Purchase Plan

In October 2019, the Company's board of directors adopted the 2019 Employee Stock Purchase Plan ("ESPP"), which became effective in November 2019. The Company initially reserved 225,188 shares of common stock for purchase under the ESPP. The number of shares of common stock reserved for issuance under the ESPP will automatically increase on the first day of January for a period of up to ten years in an amount equal to 1% of the total number of shares of the Company's common stock outstanding on the immediately preceding December 31, or a lesser number of shares determined by the Company's board of directors. Purchases are accomplished through the participation of discrete offering periods and each offering is expected to be six months in duration. For each offering period, ESPP participants will purchase shares of common stock at a price per share equal to 85% of the lesser of the fair market value of the Company's common stock on (1) the first trading day of the applicable offering period or (2) the last trading day of the applicable offering period.

Stock Options

The following table summarizes stock option activity for the year ended December 31, 2022:

	Number of Options	Weighted Average Exercise Price	Weighted Average Remaining Contractual Term	Aggregate Intrinsic Value
			(In years)	(In thousands)
Balance outstanding as of December 31, 2021	2,406,668	$ 16.46	8.1	$ 9,970
Granted	1,149,816	4.48		
Exercised	(151,061)	2.09		
Cancelled and forfeited	(243,506)	16.34		
Balance outstanding as of December 31, 2022	3,161,917	$ 12.80	7.9	$ 16,612
Exercisable as of December 31, 2022	1,460,685	$ 14.60	7.0	$ 7,320

The fair value of stock options granted for the periods presented was estimated at the date of grant using a Black-Scholes option-pricing model with the following assumptions:

	Year Ended December 31,	
	2022	2021
Expected term (years)	5.5-6.3	5.5-6.1
Expected volatility	89.9-91.0%	86.9-91.9%
Risk-free interest rate	1.6-3.9%	0.7-1.3%
Expected dividend	—	—

The weighted-average grant date fair value of stock options that were granted during the year ended December 31, 2022 and 2021 was $3.38 and $16.18 per share, respectively. As of December 31, 2022, there was $12.2 million of unrecognized stock-based compensation related to stock options granted under the 2019 Plan, which is expected to be recognized over a weighted-average period of 2.2 years.

Restricted Stock Units ("RSUs")

The Company has granted certain employees service-based RSUs that generally vest annually over a two or three-year period. The restrictions lapse over time for these service-based RSUs. In the event of termination of the holder's continuous service to the Company, any unvested portion of the service-based RSUs are cancelled. For the year ended December 31, 2022 and 2021, the Company recognized expense of $1.2 million and $0.3 million, respectively, related to the service-based RSUs.

In February 2021, the Company granted performance-based RSUs that vest as to one-third on each one-year anniversary date, subject to achievement of a development milestone and continued service to the Company. In February 2022, a portion of the performance-based RSUs vested upon achievement of the development milestone and satisfaction of the continued service condition.

In February and September 2022, the Company granted performance-based RSUs that vest during the applicable performance period, subject to the achievement of certain corporate or department targets and continued service to the Company. In September 2022, a portion of the performance-based RSUs that were granted in February 2022 vested upon achievement of specific targets and satisfaction of the continued service condition.

As of December 31, 2022, it was probable that the remaining performance conditions would be met for the Company's performance-based RSUs and expense was recognized using the accelerated attribution method. For the year ended December 31, 2022 and 2021, the Company recognized expense of $1.5 million and $0.8 million, respectively, related to performance-based RSUs.

The following table summarizes RSU activity for the year ended December 31, 2022:

	Number of RSUs	Weighted Average Fair Value at Date of Grant per Unit
Balance outstanding as of December 31, 2021	106,394	$ 23.10
Granted	1,224,391	4.61
Vested / released	(103,703)	8.61
Cancelled / forfeited	(131,344)	5.53
Balance outstanding as of December 31, 2022	1,095,738	5.77

As of December 31, 2022, there was $3.9 million of total unrecognized expense related to RSUs, which is expected to be recognized over a weighted-average period of 1.4 years.

The Company recorded stock-based compensation for the periods indicated as follows (in thousands):

	Year Ended December 31,	
	2022	2021
Research and development	$ 4,094	$ 2,966
General and administrative	6,262	5,712
Total stock-based compensation	$ 10,356	$ 8,678

9. Income Taxes

Tax Rates Applicable to the Income of the Company and its Subsidiaries

The Company is taxed according to U.S. federal and state tax laws and Israeli tax laws. The statutory tax rates applicable to the income of the Company and its subsidiaries for the periods presented are as follows:

	Year Ended December 31,	
	2022	2021
89bio, Inc.	21%	21%
89Bio Ltd.	23%	23%
89bio Management, Inc.	21%	21%
UAB 89bio Lithuania	15%	15%

The income tax (expense) benefit for the periods presented is comprised of (in thousands):

	Year Ended December 31,	
	2022	2021
Current:		
Federal	—	—
State	(3)	(2)
Foreign	(16)	(1)
Total	(19)	(3)
Deferred:		
Federal	—	150
State	—	—
Foreign	—	—
Total	—	150
Income tax (expense) benefit	(19)	147

Deferred Income Taxes

Deferred income taxes reflect the net tax effects of temporary differences between the carrying amounts of assets and liabilities for financial reporting purposes and the amounts used for income tax purposes. Significant components of the Company's deferred tax assets for the periods presented are as follows (in thousands):

	As of December 31,	
	2022	2021
U.S. net operating loss carryforwards	$ 45,002	$ 29,094
Research and development expenses	18,927	6,529
Israel net operating loss carryforwards	7,385	4,262
Stock-based compensation	4,328	1,969
Accrued expenses	317	220
Operating Lease Liability	98	—
Other	244	191
Gross deferred tax assets	76,301	42,265
Less: valuation allowance	(75,982)	(42,046)
Total deferred tax assets	$ 319	$ 219
Operating lease right-of-use asset	(100)	—
Total deferred tax liabilities	(100)	—
Net deferred tax assets	219	219

As of December 31, 2022 and 2021, the Company recorded a valuation allowance of $76.0 million and $42.0 million, respectively, in respect of deferred tax assets resulting from tax loss carryforwards and other temporary differences. Realization of deferred tax assets is dependent upon future earnings, if any, the time and amount of

which are uncertain. The Company regularly assesses the likelihood that its deferred tax assets will be recovered from future taxable income and, to the extent it believes based upon the weight of available evidence that it is more likely than not that all or a portion of deferred tax assets will not be realized, a valuation allowance is established through an adjustment to income tax expense. The valuation allowance increased by $34.0 million in 2022, which primarily relates to significant taxable losses. The Company continues to record a partial valuation allowance against the deferred tax assets in Israel due to achievement of recent profitability and the expectation of future profitability in the jurisdiction.

Available Carryforward Tax Losses and Credits

As of December 31, 2022, the Company had an accumulated tax loss carryforward of approximately $160.9 million, $169.8 million, and $32.1 million for Federal, State and Israeli tax purposes, respectively. As of December 31, 2021, the Company had an accumulated tax loss carryforward of approximately $138.5 million and $18.5 million for U.S. and Israeli tax purposes, respectively. Federal net operating losses generated after 2017 can be carried forward indefinitely but utilization will be limited to 80% of taxable income in the period that net operating losses are being utilized. Carryforward tax losses in California will begin to expire in 2041. Carryforward tax losses in Israel have no expiration date.

As of December 31, 2022 and 2021, the Company had federal research and development credit carryforwards of approximately $4.3 million and $2.1 million, respectively, which expire beginning in 2040. As of December 31, 2022 and December 31, 2021, the Company had state research and development credit carryforwards of approximately $1.8 million and $1.1 million, respectively, which will carry forward indefinitely.

Loss from Operations, Before Income Tax

The Company recorded a loss from operations, before income tax for the periods presented as follows (in thousands):

	Year Ended December 31,	
	2022	2021
United States	$ (101,938)	$ (91,141)
Lithuania	(7)	10
Israel	(62)	862
Net loss before income tax	$ (102,007)	$ (90,269)

Reconciliation of Income Tax (Expense) Benefit

The reconciliation of income tax (expense) benefit based on the statutory tax rate to the effective tax rate for the periods presented is as follows (in thousands):

	Year Ended December 31,	
	2022	2021
Income tax benefit computed at statutory rates	$ 21,429	$ 18,757
Change in valuation allowance	(33,936)	(20,111)
Foreign rate differential	1	(19)
State income taxes, net of federal benefit	5,824	—
State deferred tax true-up due to change in apportionment	6,517	—
Change in Israel effective tax rate due to the 2019 reorganization	—	(2)
Research and development credits, net of uncertain tax position	2,130	1,331
Other	(1,984)	191
Income tax (expense) benefit	$ (19)	$ 147

Utilization of U.S. federal and state net operating losses and credit carryforwards may be subject to an annual limitation provided for in Section 382 of the Internal Revenue Code and similar state codes. Any annual limitation could result in a deferral of the utilization of the net operating loss and credit carryforwards.

Unrecognized Tax Benefits

A reconciliation of the unrecognized tax benefits for the year ended December 31, 2022 and 2021 is as follows (in thousands):

	As of December 31,	
	2022	2021
Balance beginning of year	851	329
Decrease related to prior year positions	(19)	(35)
Increase related to current year positions	752	557
Balance end of year	1,584	851

During the year ended December 31, 2022 and 2021, the amount of gross unrecognized tax benefits increased by $0.7 million and $0.5 million, respectively. If the total amount of unrecognized tax benefits was recognized, it would not have an impact to the effective tax rate as it would be offset by the reversal of related deferred tax assets which are subject to a full valuation allowance.

The Company recognizes interest and penalties related to uncertain tax positions as part of the income tax provision. As of December 31, 2022 and 2021, such interest and penalties were not material.

The Company is subject to taxation in the United States, California, Colorado, North Carolina and several foreign jurisdictions. To date, the Company has not been subject to any federal or state income tax audits. The Company is currently under examination by the Israeli tax authorities for 2018 and 2019. As of December 31, 2022, all tax years remain open to examination.

On August 9, 2022 and August 16, 2022, the Creating Helpful Incentives to Produce Semiconductors (“CHIPS”) Act and the Inflation Reduction Act (“IRA”), respectively, were signed into law. The CHIPS Act and IRA contain among other things, some income tax provisions that establish a corporate alternative minimum tax and provide tax incentives for semiconductor manufacturing and research. The Company has evaluated the current legislation and at this time, does not anticipate either to have a material impact on its financial statements.

The Tax Cuts and Jobs Act (“TCJA”) included a change in the treatment of research and development (“R&D”) expenditures for tax purposes under Section 174. Effective for tax years beginning after December 31, 2021, specified R&D expenditures must undergo a 5-year amortization period for domestic spend and a 15-year amortization period for foreign spend. Prior to the effective date (2021 tax year and prior), taxpayers were able to immediately expense R&D costs under Section 174(a) or had the option to capitalize and amortize R&D expenditures over a 5-year recovery period under Section 174(b). The Company has evaluated the current legislation at this time and prepared the provision by following the treatment of R&D expenditures for tax purposes under Section 174.

10. Net Loss Per Share

The following outstanding potentially dilutive common stock equivalents have been excluded from the calculation of diluted net loss per share for the periods indicated due to their anti-dilutive effect:

	Year Ended December 31,	
	2022	2021
Stock options to purchase common stock	3,161,917	2,406,668
Unvested restricted stock units	1,095,738	106,394
Warrants to purchase common stock[1]	13,166,283	58,923
Total	17,423,938	2,571,985

[1] The table above excludes pre-funded warrants issued in connection with the July 2022 public offering (see Note 7).

11. Subsequent Events

2023 Loan Agreement

In January 2023, the Company executed the 2023 Loan Agreement with the new lenders named therein. The 2023 Loan Agreement provides up to $100.0 million in aggregate principal in term loans, consisting of a first tranche of $25.0 million that was funded at closing, two subsequent tranches totaling $25.0 million that may be funded upon the achievement of certain time-based, clinical and regulatory milestones, and a fourth tranche of up to $50.0 million that may be funded upon discretionary approval by the lenders.

The term loans under the 2023 Loan Agreement mature on January 1, 2027. The maturity date may be extended to July 1, 2027, provided that the second and third tranches are funded and the Company achieves certain other financing milestones. The term loans bear interest equal to the greater of (i) 8.45% and (ii) the sum of (a) the Prime Rate as reported in The Wall Street Journal plus (b) 2.25%. Consecutive monthly payments of interest commence in February 2023 and consecutive monthly payments of principal commence in February 2025, or February 2026 provided that certain extension milestones are achieved.

2021 Loan Agreement

In January 2023, the first tranche of $25.0 million that was funded pursuant to the 2023 Loan Agreement was primarily used to repay the Company’s outstanding obligations under the 2021 Loan Agreement, including the total principal amount outstanding as of December 31, 2022 of $20.0 million, the final payment fee of $1.0 million and an early prepayment fee of $0.4 million (see Note 6).

ATM Facility

In January and February 2023, the Company received aggregate proceeds of $13.4 million, net of commissions from sales of 968,000 shares of its common stock pursuant to the ATM Facility (see Note 7).

On February 15, 2023, the Company entered into Amendment No. 1 to the Sales Agreement with the Sales Agent, pursuant to which the Company may offer and sell up to $150.0 million shares of its common stock, from time to time, through the ATM Facility (see Note 7).

Banking Relationship with SVB

The Company has a banking relationship with SVB. On March 10, 2023, SVB was closed by the California Department of Financial Protection and Innovation, which appointed the Federal Deposit Insurance Corporation ("FDIC") as receiver. On March 12, 2023, the Federal Reserve Board approved actions enabling the FDIC to complete its resolution of SVB in a manner that fully protects all depositors. Based on the foregoing and the Company’s analysis of the components of its relationship with SVB, the Company does not expect these events to have a material impact on the Company’s consolidated financial statements.

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

As of December 31, 2022, our management, with the participation and supervision of our principal executive officer and our principal financial officer, evaluated our disclosure controls and procedures (as defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act). The term "disclosure controls and procedures," as defined in Rules 13a-15(e) and 15d-15(e) under 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 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. 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 this evaluation, our principal executive officer and our principal financial officer concluded that our disclosure controls and procedures were effective as of December 31, 2022 to provide reasonable assurance that information we are required to disclose in reports that we file or submit under the Exchange Act is recorded, processed, summarized, and reported within the time periods specified in SEC rules and forms, and that such information is accumulated and communicated to our management, including our principal executive officer and our principal financial officer, as appropriate, to allow timely decisions regarding required disclosure.

Changes in Internal Control over Financial Reporting

There were no changes in our internal control over financial reporting (as defined in Rules 13a-15(f) and 15d-15(f) under the Exchange Act) occurred during the quarter ended December 31, 2022 that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

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 Rules 13a-15(f) under the Exchange Act). Internal control over financial reporting is a process designed under the supervision and with the participation of our management, including our principal executive officer and our principal financial officer, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles in the United States.

As of December 31, 2022, our management assessed the effectiveness of our internal control over financial reporting using the criteria set forth by the Committee of Sponsoring Organizations of the Treadway Commission in Internal Control-Integrated Framework ("2013 Framework"). Based on this assessment, our management concluded that our internal control over financial reporting was effective as of December 31, 2022.

Attestation Report of Registered Public Accounting Firm

As an emerging growth company, we are not required to provide and this Annual Report on Form 10-K does not include an attestation report on our internal control over financial reporting issued by the Company's independent registered public accounting firm. Our auditors will not be required to formally opine on the effectiveness of our internal control over financial reporting pursuant to Section 404(b) of the Sarbanes-Oxley Act of 2002 until we are no longer an emerging growth company, as defined in the Jumpstart Our Business Startups Act of 2012, and are no longer a non-accelerated filer.

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.

The information required by this Item 10 is incorporated herein by reference to information in our proxy statement for our 2023 Annual Meeting of Stockholders (the "2023 Proxy Statement"), which we expect to be filed with the SEC within 120 days of the end of our fiscal year ended December 31, 2022, including under the heading "Directors, Executive Officers and Corporate Governance."

We have adopted a written code of business conduct and ethics that applies to our directors, officers and employees, including our principal executive officer, principal financial officer, principal accounting officer or controller, or persons performing similar functions. A copy of the code is available on our website located at www.89bio.com, under "Corporate Governance." We intend to disclose on our website any amendments to, or waivers from, the code of business conduct and ethics that are required to be disclosed pursuant to the disclosure requirements of Item 5.05 of Form 8-K within four business days following the date of the amendment or waiver.

Item 11. Executive Compensation.

The information required by this Item 11 is incorporated herein by reference to information in our 2023 Proxy Statement, including under headings "Executive Compensation" and "Directors, Executive Officers and Corporate Governance."

Item 12. Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters.

The information required by this Item 12 is incorporated herein by reference to information in our 2023 Proxy Statement, including under headings "Security Ownership of Certain Beneficial Owners and Management" and "Executive Compensation-Securities Authorized for Issuance Under Equity Compensation Plans."

Item 13. Certain Relationships and Related Transactions, and Director Independence.

The information required by this Item 13 is incorporated herein by reference to information in our 2023 Proxy Statement, including under headings "Directors, Executive Officers and Corporate Governance" and "Certain Relationships and Related Party Transactions."

Item 14. Principal Accountant Fees and Services.

The information required by this Item 14 is incorporated herein by reference to information in our 2023 Proxy Statement, including under the heading "Ratification of Selection of Independent Registered Public Accounting Firm."

PART IV

Item 15. Exhibits, Financial Statement Schedules.

(a) The following documents are filed as a part of this report:

(1) Financial Statements

See Index to Consolidated Financial Statements at Part II Item 8 “Financial Statements and Supplementary Data.”

(2) Financial Statement Schedules

The financial statement schedules are omitted as they are either not applicable or the information required is presented in the financial statements and notes thereto under Part II Item 8 “Financial Statements and Supplementary Data.”

(3) Exhibits:

Exhibit Index

Exhibit Number	Description
2.1	Contribution and Exchange Agreement, dated as of September 17, 2019, by and among 89Bio Ltd., the Company and its shareholders (filed with the SEC as Exhibit 2.1 to the Company's Form S-1 filed on October 11, 2019)
3.1	Second Amended and Restated Certificate of Incorporation of the Company (filed with the SEC as Exhibit 3.1 to the Company's Current Report on Form 8-K filed on November 15, 2019)
3.2	Second Amended and Restated Bylaws of the Company (filed with the SEC as Exhibit 3.2 to the Company's Current Report on Form 8-K filed on November 15, 2019)
4.1	Specimen common stock certificate of the Company (filed with the SEC as Exhibit 4.1 to the Company's Form S-1/A filed on October 28, 2019)
4.2*	Description of Securities
4.3	Form of Warrant to Purchase Common Stock for Silicon Valley Bank (filed with SEC as Exhibit 4.1 to the Company's Current Report on Form 8-K filed on April 13, 2020)
4.4	Form of Warrant to Purchase Common Stock for Silicon Valley Bank (filed with the SEC as Exhibit 4.1 to the Company's Current Report on Form 8-K filed on June 4, 2021)
4.5	Form of Warrant (filed with the SEC as Exhibit 4.1 to the Company's Current Report on Form 8-K filed on July 1, 2022)
4.6	Form of Pre-Funded Warrant (filed with the SEC as Exhibit 4.2 to the Company's Current Report on Form 8-K filed on July 1, 2022)
4.7	Form of Warrant to Purchase Common Stock for K2 HealthVentures LLC (filed with the SEC as Exhibit 4.1 to the Company's Current Report on Form 8-K/A filed on February 2, 2023)
10.1	Sales Agreement, dated March 25, 2021, by and among the Company, SVB Securities LLC and Cantor Fitzgerald & Co. (filed with the SEC as Exhibit 1.2 to the Company's Form S-3 filed on March 25, 2021)
10.2	Amendment No. 1 to Sales Agreement, dated February 15, 2023, by and among the Company, SVB Securities LLC and Cantor Fitzgerald & Co. (filed with the SEC as Exhibit 1.2 to the Company's Current Report on Form 8-K filed on February 16, 2023)
10.3+	Form of Indemnification Agreement for directors and executive officers (filed with the SEC as Exhibit 10.1 to the Company's Form S-1 filed on October 11, 2019)
10.4+	Amended and Restated 2019 Equity Incentive Plan and form of agreements thereunder (filed with the SEC as Exhibit 10.2 to the Company's Form S-1/A filed on October 28, 2019)
10.5+	2019 Employee Stock Purchase Plan (filed with the SEC as Exhibit 10.3 to the Company's Form S-1/A filed on October 28, 2019)
10.6+	Executive Employment Offer Letter, dated April 15, 2020, by and between the Company and Rohan Palekar (filed with the SEC as Exhibit 10.1 to the Company's Current Report on Form 8-K filed on May 4, 2020)
10.7+	Executive Employment Offer Letter, dated April 15, 2020, by and between the Company and Hank Mansbach (filed with the SEC as Exhibit 10.3 to the Company's Current Report on Form 8-K filed on May 4, 2020)
10.8+	Executive Employment Offer Letter, dated April 15, 2020, by and between the Company and Quoc Le-Nguyen (filed with the SEC as Exhibit 10.4 to the Company's Current Report on Form 8-K filed on May 4, 2020)
10.9+	Executive Employment Offer Letter, dated April 15, 2020, by and between the Company and Ryan Martins (filed with the SEC as Exhibit 10.2 to the Company's Current Report on Form 8-K filed on May 4, 2020)

Exhibit Number	Description
10.10+	Director Offer Letter, dated July 1, 2018, by and between 89Bio Ltd. and Michael Hayden (filed with the SEC as Exhibit 10.9 to the Company's Form S-1 filed on October 11, 2019)
10.11+	Non-Employee Director Compensation Policy (filed with the SEC as Exhibit 10.1 to the Company's Quarterly Report on Form 10-Q filed on November 13, 2020)
10.12+	Asset Transfer and License Agreement—FGF21 by and among 89Bio Ltd., ratiopharm GmbH, Teva Branded Pharmaceutical Products R&D, Inc. and Teva Pharmaceutical Industries Ltd, dated as of April 16, 2018 (filed with the SEC as Exhibit 10.11 to the Company's Form S-1 filed on October 11, 2019)
10.13+	Sublicense Agreement by and between 89Bio Ltd. and ratiopharm GmbH, dated as of April 16, 2018 (filed with the SEC as Exhibit 10.13 to the Company's Form S-1 filed on October 11, 2019)
10.14+	Master Services Agreement by and between 89Bio Ltd. and Biotechpharma UAB, dated as of May 7, 2018, as amended (filed with the SEC as Exhibit 10.14 to the Company's Form S-1 filed on October 11, 2019)
10.15	Office Lease by and between 89bio, Inc. and King Family Irrevocable Trust, dated as of December 5, 2019 (filed with the SEC as Exhibit 10.15 to the Company's Annual Report on Form 10-K filed on March 18, 2020)
10.16	First Amendment to Office Lease, dated as of July 27, 2021, by and between King Family Irrevocable Trust and the Company (filed with the SEC as Exhibit 10.1 to the Company's Quarterly Report on Form 10-Q filed on November 12, 2021)
10.17	Second Amendment to Office Lease, dated as of August 31, 2022, by and between King Family Irrevocable Trust and the Company (filed with the SEC as Exhibit 10.1 to the Company's Quarterly Report on Form 10-Q filed on November 10, 2022)
10.18	Loan and Security Agreement, dated as of January 4, 2023, among the Company, 89bio Management, Inc., 89Bio Ltd., K2 HealthVentures LLC and Ankura Trust Company, LLC (filed with the SEC as Exhibit 10.1 to the Company's Current Report on Form 8-K filed January 6, 2023)
21.1+	List of subsidiaries (filed with the SEC as Exhibit 21.1 to the Company's Form S-1 filed on October 11, 2019)
23.1*	Consent of Independent Registered Public Accounting Firm
24.1*	Power of Attorney
31.1*	Certification of Principal Executive Officer Pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934
31.2*	Certification of Principal Financial Officer Pursuant to Rules 13a-14(a) and 15d-14(a) under the Securities Exchange Act of 1934
32.1#	Certification of Principal Executive Officer and Principal Financial Officer Pursuant to 18 U.S.C. Section 1350
101.INS	Inline XBRL Instance Document
101.SCH	Inline XBRL Taxonomy Extension Schema Document
101.CAL	Inline XBRL Taxonomy Extension Calculation Linkbase Document
101.DEF	Inline XBRL Taxonomy Extension Definition Linkbase Document
101.LAB	Inline XBRL Taxonomy Extension Label Linkbase Document
101.PRE	Inline XBRL Taxonomy Extension Presentation Linkbase Document
104	Cover Page Interactive Data File

* Filed herewith.
+ Indicates management contract or compensatory plan.
† Portions of the exhibit have been omitted for confidentiality purposes.
# Furnished herewith and not deemed to be "filed" for purposes of Section 18 of the Exchange Act, and shall not be deemed to be incorporated by reference into any filing under the Securities Act of 1933, as amended, or the Exchange Act.

Item 16. Form 10-K Summary.

None.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, as amended, the Registrant has duly caused this Report to be signed on its behalf by the undersigned, thereunto duly authorized**.**

89bio, Inc.

Date: March 14, 2023 By: /s/ Rohan Palekar

Rohan Palekar
Chief Executive Officer and Director
(principal executive officer)

Date: March 14, 2023 By: /s/ Ryan Martins

Ryan Martins
Chief Financial Officer
(principal financial and accounting officer)

POWER OF ATTORNEY

KNOW ALL PERSONS BY THESE PRESENTS, that each person whose signature appears below hereby constitutes and appoints Rohan Palekar, and Ryan Martins, and each of them, the true and lawful attorneys-in-fact and agents of the undersigned, with full power of substitution and resubstitution, for and in the name, place and stead of the undersigned, to sign in any and all capacities (including, without limitation, the capacities listed below), this Annual Report on Form 10-K, any and all amendments thereto, and to file the same, with all exhibits thereto, and all other documents in connection therewith, with the Securities and Exchange Commission, and hereby grants to such attorneys-in-fact and agents, and each of them, full power and authority to do and perform each and every act and anything necessary to be done to enable the registrant to comply with the provisions of the Securities Exchange Act and all the requirements of the Securities and Exchange Commission, as fully to all intents and purposes as the undersigned might or could do in person, hereby ratifying and confirming all that said attorneys-in-fact and agents, or any of them, or their or his or her substitute, or substitutes, may lawfully do or cause to be done by virtue hereof.

Pursuant to the requirements of the Securities Exchange Act of 1934, as amended, this Report has been signed below by the following persons on behalf of the Registrant in the capacities and on the dates indicated.

Name	Title	Date
/s/ Rohan Palekar **Rohan Palekar**	Chief Executive Officer and Director (*principal executive officer*)	March 14, 2023
/s/ Ryan Martins **Ryan Martins**	Chief Financial Officer (*principal financial and accounting officer*)	March 14, 2023
/s/ Steven Altschuler **Steven Altschuler, M.D.**	Director	March 14, 2023
/s/ Derek DiRocco **Derek DiRocco, Ph.D.**	Director	March 14, 2023
/s/ Gregory Grunberg **Gregory Grunberg, M.D.**	Director	March 14, 2023
/s/ Michael Hayden **Michael Hayden, M.B., Ch.B., Ph.D.**	Director	March 14, 2023
/s/ Kathleen D. LaPorte **Kathleen D. LaPorte**	Director	March 14, 2023
/s/ Lota Zoth **Lota Zoth, C.P.A.**	Director	March 14, 2023
/s/ Edward Morrow Atkinson III **Edward Morrow Atkinson III**	Director	March 14, 2023

Exhibit 4.2

DESCRIPTION OF REGISTRANT'S SECURITIES REGISTERED PURSUANT TO SECTION 12 OF THE SECURITIES EXCHANGE ACT OF 1934

The following description of our capital stock is intended as a summary only and therefore is not a complete description of our capital stock. This description is based upon, and is qualified by reference to, our second amended and restated certificate of incorporation (the "Amended Certificate"), our second amended and restated bylaws (the "Amended Bylaws") and applicable provisions of Delaware corporate law. You should read our Amended Certificate and Amended Bylaws, which are filed as exhibits to our Annual Report on Form 10-K, to which this exhibit is also appended.

Our authorized capital stock consists of 100,000,000 shares of common stock and 10,000,000 shares of preferred stock.

Common Stock

Our Amended Certificate authorizes the issuance of up to 100,000,000 shares of our common stock. All outstanding shares of our common stock are validly issued, fully paid and nonassessable.

The holders of our common stock are entitled to one vote per share on all matters submitted to a vote of stockholders. A majority vote of the shares present in person or represented by proxy and entitled to vote on the subject matter is required for the holders of our common stock to take action on all matters (except for election of directors (as discussed below)), except as otherwise required by law, our Amended Certificate or our Amended Bylaws. Our Amended Certificate does not provide for cumulative voting in the election of directors. The holders of our common stock will receive ratably any dividends declared by our board of directors out of funds legally available therefor. In the event of our liquidation, dissolution or winding-up, the holders of our common stock will be entitled to share ratably in all assets remaining after payment of or provision for any liabilities.

Preferred Stock

Under the terms of our Amended Certificate, our board of directors has the authority, without further action by our stockholders, to issue up to 10,000,000 shares of preferred stock in one or more series, to establish from time to time the number of shares to be included in each such series, to fix the dividend, voting and other rights, preferences and privileges of the shares of each wholly unissued series and any qualifications, limitations or restrictions thereon, and to increase or decrease the number of shares of any such series, but not below the number of shares of such series then outstanding.

Our board of directors may authorize the issuance of preferred stock with voting or conversion rights that could adversely affect the voting power or other rights of the holders of our common stock. The issuance of preferred stock, while providing flexibility in connection with possible acquisitions and other corporate purposes, could, among other things, have the effect of delaying, deferring or preventing a change in our control and may adversely affect the market price of our common stock and the voting and other rights of the holders of our common stock.

Anti-Takeover Effects of Our Amended Certificate, Amended Bylaws and Delaware Law

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

- ***Issuance of undesignated preferred stock:*** Under our Amended Certificate, our board of directors has the authority, without further action by the stockholders, to issue up to 10,000,000 shares of undesignated preferred stock with rights and preferences, including voting rights, designated from time to time by our board of directors. The existence of authorized but unissued shares of preferred stock enables our board of

directors to make it more difficult to attempt to obtain control of us by means of a merger, tender offer, proxy contest or otherwise.

- ***Classified board:*** Our Amended Certificate establishes a classified board of directors consisting of three classes of directors, with staggered three-year terms. Only one class of directors will be elected at each annual meeting of our stockholders, with the other classes continuing for the remainder of their respective three-year terms. This provision may have the effect of delaying a change in control of our board of directors.

- ***Election and removal of directors and board vacancies:*** Our Amended Bylaws provide that directors will be elected by a plurality vote. Our Amended Certificate and Amended Bylaws also provide that our board of directors has the right to increase or decrease the size of the board and to fill vacancies on the board. Directors may be removed only for cause by the affirmative vote of the holders of at least 66⅔% of the votes that all our stockholders would be entitled to cast in an annual election of directors. Only our board of directors is authorized to fill vacant directorships. In addition the number of directors constituting our board of directors may be set only by resolution adopted by a majority vote of the directors then in office. These provisions prevent stockholders from increasing the size of our board of directors and gaining control of our board of directors by filling the resulting vacancies with its own nominees.

- ***Requirements for advance notification of stockholder nominations and proposals:*** Our Amended Bylaws establish advance notice procedures with respect to stockholder proposals and the nomination of candidates for election as directors that specify certain requirements as to the timing, form and content of a stockholder's notice. Business that may be conducted at an annual meeting of stockholders will be limited to those matters properly brought before the meeting. These provisions may make it more difficult for our stockholders to bring matters before our annual meeting of stockholders or to nominate directors at annual meetings of stockholders.

- ***No written consent of stockholders:*** Our Amended Certificate provides that all stockholder actions be taken by a vote of the stockholders at an annual or special meeting, and that stockholders may not take any action by written consent in lieu of a meeting. This limit may lengthen the amount of time required to take stockholder actions and would prevent the amendment of our Amended Bylaws or removal of directors by our stockholders without holding a meeting of stockholders**.**

- ***No stockholder ability to call special meetings:*** Our Amended Certificate and Amended Bylaws provide that only a majority of the members of our board of directors then in office may be able to call special meetings of stockholders and only those matters set forth in the notice of the special meeting may be considered or acted upon at a special meeting of stockholders.

- ***Amendments to certificate of incorporation and bylaws:*** Any amendment to our Amended Certificate will be required to be approved by a majority of our board of directors as well as, if required by law or the Amended Certificate, a majority of the outstanding shares entitled to vote on the amendment and a majority of the outstanding shares of each class entitled to vote thereon as a class, except that the amendment of provisions to board classification, stockholder action, certificate amendments, and liability of directors must be approved by not less than 66⅔% of the outstanding shares entitled to vote on the amendment, voting together as a single class. Any amendment to our Amended Bylaws must be approved by either a

majority of our board of directors or not less than 66⅔% of the outstanding shares entitled to vote on the amendment, voting together as a single class.

These provisions are designed to enhance the likelihood of continued stability in the composition of our board of directors and its policies, to discourage certain types of transactions that may involve an actual or threatened acquisition of us and to reduce our vulnerability to an unsolicited acquisition proposal. We also designed these provisions to discourage certain tactics that may be used in proxy fights. However, these provisions could have the effect of discouraging others from making tender offers for our shares and, as a consequence, they may also reduce fluctuations in the market price of our shares that could result from actual or rumored takeover attempts.

Section 203 of the Delaware General Corporation Law

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

Choice of Forum

Our Amended Certificate requires that the Court of Chancery of the State of Delaware be the exclusive forum for the following types of actions or proceedings under Delaware statutory or common law: (1) any derivative action or proceeding brought on our behalf; (2) any action asserting a breach of fiduciary duty owed by any director, officer or other employee to us or our stockholders; (3) any action asserting a claim against us or any director or officer or other employee arising pursuant to the Delaware General Corporation Law, our Amended Certificate or Amended Bylaws; or (4) any action asserting a claim against us or any director or officer or other employee that is governed by the internal affairs doctrine. This provision would not apply to claims brought to enforce a duty or liability created by the Securities Exchange Act of 1934, as amended, or any other claim for which the federal courts have exclusive jurisdiction. Our Amended Certificate provides further that the federal district courts of the United States will be the exclusive forum for resolving any complaint asserting a cause of action arising under the Securities Act, subject to and contingent upon a final adjudication in the State of Delaware of the enforceability of such exclusive forum provision. Although we believe these provisions benefit us by providing increased consistency in the application of Delaware law for the specified types of actions and proceedings, the provisions may have the effect of discouraging lawsuits against us or our directors or officers.

Transfer Agent and Registrar

American Stock Transfer and Trust Company, LLC serves as the transfer agent and registrar for our common stock.

Listing

Our common stock is listed on The Nasdaq Global Market under the symbol "ETNB."

Exhibit 23.1

Consent of Independent Registered Public Accounting Firm

We consent to the incorporation by reference in the registration statements (No. 333-269471) on Form S-3 and (Nos.333-263838, 333-254683, 333-237263, 333-235577) on Form S-8 of our report dated March 14, 2023, with respect to the consolidated financial statements of 89bio, Inc.

/s/ KPMG LLP

San Francisco, California
March 14, 2023

Exhibit 31.1

CERTIFICATION PURSUANT TO
RULES 13a-14(a) AND 15d-14(a) UNDER THE SECURITIES EXCHANGE ACT OF 1934,
AS ADOPTED PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002

I, Rohan Palekar, certify that:

1. I have reviewed this Annual Report on Form 10-K of 89bio, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

   (a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   (b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

   (c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   (d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

   (a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   (b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 14, 2023

By: /s/ Rohan Palekar

Rohan Palekar
Chief Executive Officer
(principal executive officer)

Exhibit 31.2

CERTIFICATION PURSUANT TO
RULES 13a-14(a) AND 15d-14(a) UNDER THE SECURITIES EXCHANGE ACT OF 1934,
AS ADOPTED PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002

I, Ryan Martins, certify that:

1. I have reviewed this Annual Report on Form 10-K of 89bio, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) and internal control over financial reporting (as defined in Exchange Act Rules 13a-15(f) and 15d-15(f)) for the registrant and have:

   (a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

   (b) Designed such internal control over financial reporting, or caused such internal control over financial reporting to be designed under our supervision, to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles;

   (c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

   (d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

   (a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

   (b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

Date: March 14, 2023

By: /s/ Ryan Martins

Ryan Martins
Chief Financial Officer
(principal financial and accounting officer)

Exhibit 32.1

CERTIFICATION PURSUANT TO
18 U.S.C. SECTION 1350, AS ADOPTED PURSUANT TO
SECTION 906 OF THE SARBANES-OXLEY ACT OF 2002

In connection with the Annual Report of 89bio, Inc. (the "Company") on Form 10-K for the year ending December 31, 2022, as filed with the Securities and Exchange Commission on the date hereof (the "Report"), each of the undersigned officers of the Company hereby certifies, pursuant to 18 U.S.C. § 1350, as adopted pursuant to § 906 of the Sarbanes-Oxley Act of 2002, that to the best of his knowledge:

(1) The Report fully complies with the requirements of section 13(a) or 15(d) of the Securities Exchange Act of 1934; and

(2) The information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Date: March 14, 2023 By: /s/ Rohan Palekar

Rohan Palekar
Chief Executive Officer
(principal executive officer)

Date: March 14, 2023 By: /s/ Ryan Martins

Ryan Martins
Chief Financial Officer
(principal financial and accounting officer)

The foregoing certification is being furnished solely to accompany the Report pursuant to 18 U.S.C. § 1350, and is not being filed for purposes of Section 18 of the Securities Exchange Act of 1934, and is not to be incorporated by reference into any filing of the Company, whether made before or after the date hereof, regardless of any general incorporation language in such filing.
Note: A signed original of this written statement required by § 906 has been provided to 89bio, Inc. and will be retained by 89bio, Inc. and furnished to the Securities and Exchange Commission or its staff upon request.