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, 2018

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 001-36510

ZAFGEN, INC.

(Exact name of registrant as specified in its charter)

Delaware	**20-3857670**
(State or other jurisdiction of incorporation or organization)	**(IRS Employer Identification No.)**

Zafgen, Inc.
175 Portland Street, 4th Floor
Boston, Massachusetts 02114
(Address of principal executive offices, including zip code)
Registrant's Telephone Number, Including Area Code:
(617) 622-4003
Securities registered pursuant to Section 12(b) of the Act:

Common Stock, $0.001 Par Value	**The NASDAQ Global Market**
(Title of each class)	**(Name of each exchange on which registered)**

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 Section 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 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 if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ☒

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

Large accelerated filer	☐	Accelerated filer	☒
Non-accelerated filer	☐	Emerging growth company	☒
Smaller reporting 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 is a shell company (as defined in Rule 12b-2 of the Exchange Act). Yes ☐ No ☒

The aggregate market value of Common Stock held by non-affiliates of the registrant computed by reference to the price of the registrant's Common Stock as of June 29, 2018, the last business day of the registrant's most recently completed second fiscal quarter, was approximately $201.8 million (based on the last reported sale price on the Nasdaq Global Market as of such date). As of March 1, 2019, there were 37,315,118 shares of the registrant's Common Stock, $0.001 par value per share, outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

The registrant intends to file a definitive proxy statement pursuant to Regulation 14A within 120 days of the end of the fiscal year ended December 31, 2018. Portions of such definitive proxy statement are incorporated by reference into Part III of this Annual Report on Form 10-K.

ZAFGEN, INC.

ANNUAL REPORT ON FORM 10-K

For the Year Ended December 31, 2018

PART I

This Annual Report on Form 10-K, or Annual Report, contains forward-looking statements that involve risks and uncertainties. We make such forward-looking statements pursuant to the safe harbor provisions of the Private Securities Litigation Reform Act of 1995 and other federal securities laws. All statements other than statements of historical facts contained in this Annual Report are forward-looking statements. In some cases, you can identify forward-looking statements by terminology such as "may," "will," "should," "expects," "intends," "plans," "anticipates," "believes," "estimates," "predicts," "potential," "continue" or the negative of these terms or other comparable terminology. These forward-looking statements include, but are not limited to, statements about:

- the accuracy of our estimates regarding expenses, future revenues, cash forecasts and capital requirements;
- our ability to successfully file and have our investigational new drug application, or IND, for ZGN-1258, ZGN-1345 and/or ZGN-1061 go into effect, including our ability to overcome the full clinical hold placed on ZGN-1061 by the U.S. Food and Drug Administration, or FDA;
- our ability to continue to evaluate ZGN-1258 and to advance the program in nonclinical and clinical development following an unexpected finding in muscle tissue in rodent toxicology studies;
- our ability to successfully advance ZGN-1061 and our other product candidates into and through all clinical trials to enable submission of a new drug application, or NDA;
- our ability to gain regulatory approval and to successfully commercialize our product candidates;
- our ability to develop supportive clinical and nonclinical data for partnering and to successfully partner ZGN-1061 before commencing Phase 3 clinical development;
- our ability to advance our earlier-stage product candidates, including ZGN-1258 (if our further evaluation of ZGN-1258 warrants continued development and commercialization) or ZGN-1345, into clinical development and successfully complete clinical trials;
- our ability to dissociate effects of methionine aminopeptidase 2, or MetAP2, inhibitors from pro-thrombotic effects or other adverse events observed in clinical development of our first-generation compound, beloranib;
- our ability to distinguish ZGN-1061, ZGN-1258, ZGN-1345 and other novel MetAP2 inhibitors relative to our first-generation compound;
- regulatory and political developments in the United States and foreign countries;
- the performance of our third-party contract manufacturers and clinical research organizations;
- our ability to obtain and maintain intellectual property protection for our proprietary assets;
- the size of the potential markets for our product candidates and our ability to serve those markets;
- the rate and degree of market acceptance of our product candidates for any indication once approved;
- our ability to obtain additional financing when needed;
- the success of competing products that are or become available for the indications that we are pursuing;
- the loss of our executive, medical and development teams; and
- other risks and uncertainties, including those listed under Part I, Item 1A. Risk Factors.

Any forward-looking statements in this Annual Report reflect our current views with respect to future events or to our future financial performance and involve known and unknown risks, uncertainties and other factors that may cause our actual results, performance or achievements to be materially different from any future results, performance or achievements expressed or implied by these forward-looking statements. Factors that may cause actual results to differ materially from current expectations include, among other things, those listed under Part I, Item 1A. Risk Factors and elsewhere in this Annual Report. Given these uncertainties, you should not place undue reliance on these forward-looking statements. Except as required by law, we assume no obligation to update or revise these forward-looking statements for any reason, even if new information becomes available in the future.

This Annual Report also contains estimates, projections and other information concerning our industry, our business, and the markets for certain diseases, including data regarding the estimated size of those markets, and the incidence and prevalence of certain medical conditions. Information that is based on estimates, forecasts, projections, market research or similar methodologies is inherently subject to uncertainties and actual events or circumstances may differ materially from events and circumstances reflected in this information. Unless otherwise expressly stated, we obtained this industry, business, market and other data from reports, research surveys, studies and similar data prepared by market research firms and other third parties, industry, medical and general publications, government data and similar sources.

ITEM 1. BUSINESS

Overview

We are a clinical-stage biopharmaceutical company leveraging our proprietary methionine aminopeptidase 2, or MetAP2, biology platform to develop novel therapies for patients affected by complex metabolic diseases. We have pioneered the study of MetAP2 inhibitors in both common and rare metabolic disorders and we are currently advancing programs for type 2 diabetes, Prader-Willi syndrome, or PWS, and liver diseases.

Our lead product candidate is ZGN-1061, a novel fumagillin-class MetAP2 inhibitor administered by subcutaneous injection, which is currently being profiled for its utility in the treatment of type 2 diabetes. Type 2 diabetes is a prevalent, chronic, progressive, multifactorial disease that leads to increased microvascular and macrovascular disease, and as such, increases risk of death from cardiovascular disease, stroke, and kidney failure. Type 2 diabetes is also a leading cause of lower-limb amputation and blindness. Existing treatments, while effective in reducing blood glucose levels, fail to reduce progression of the disease, which is driven by loss of function of insulin-producing beta cells and by loss of sensitivity to insulin action. It is estimated that approximately one-third of patients with type 2 diabetes progress to needing insulin (recently estimated to be a $20.0 billion market based on annual sales). New therapies are needed to improve glycemic control and reduce comorbidities of type 2 diabetes.

We conducted a Phase 2 clinical trial for ZGN-1061 in Australia and New Zealand, which was designed to evaluate safety, tolerability, and glucose-lowering efficacy in patients with type 2 diabetes otherwise poorly controlled with non-insulin agents. The clinical trial met all of its primary objectives at the 1.8 mg dose, which included glycemic control, or change in A1C, and safety and tolerability. The 12-week data demonstrated that treatment with the 1.8 mg dose of ZGN-1061 produced substantially more improvement in A1C than a placebo dose. Progressive and notable reduction in body weight also occurred in patients treated with the highest dose tested (1.8 mg) versus placebo. The data showed a favorable tolerability profile for ZGN-1061, with no treatment-related serious adverse events and no cardiovascular, or CV, safety signals observed. Adverse events were primarily mild or moderate in severity, with no noted trends by dose or type of adverse event reported. We expect to report full results of the Phase 2 clinical trial at an upcoming medical meeting in 2019.

We received a letter from the FDA placing a full clinical hold on the investigational new drug application, or IND, for the first U.S. clinical trial of ZGN-1061. The FDA cited the possibility of CV safety risk based on our prior compound and outlined multiple potential paths for moving forward, including nonclinical or clinical options, to address these concerns in the ongoing development of ZGN-1061. We are assessing these options and a possible path forward and plan to request a Type A meeting with the FDA. The ex-U.S. Phase 1 and Phase 2 clinical trials of ZGN-1061 have been completed with no CV safety signals.

We have also initiated development of a second MetAP2 development candidate, ZGN-1258, which is administered by subcutaneous injection. We initiated IND enabling nonclinical activities in the first quarter of 2018, in preparation for filing an IND with the FDA. However, in March 2019, we announced our decision to suspend plans to file an IND for ZGN-1258 in order to evaluate an unexpected finding in muscle tissue in four- and six-month long-term rodent toxicology studies. Nonclinical data showed degeneration and other anomalies in rat muscle tissue to different degrees in both vehicle and dose arms of the studies. The effects were absent from other animal species in long term models, and importantly, this observed finding is specific to ZGN-1258 and is not related to effects seen with any prior compound. We are taking the necessary steps to assess the unexpected effects we observed. We will continue to evaluate ZGN-1258, as well as explore other potential options within our portfolio of MetAP2 inhibitors, to address the devastating hyperphagia experienced by those with PWS. We continue to have a commitment to people with PWS and their families and we will continue to evaluate ZGN-1258 as well as explore other potential options within our portfolio of MetAP2 inhibitors.

PWS is a rare and complex genetic disorder characterized by physiologic, cognitive and behavioral symptoms including hyperphagia, uncontrollable hunger and its related behaviors, and obesity. Published population studies estimate that the prevalence of PWS in the United States and in the European Union, or EU, ranges from 1 in 8,000 to 1 in 50,000.

The physiological drive to eat in patients with PWS is so powerful that they will go to great lengths to eat large quantities of food, even if it is spoiled, indigestible or unpalatable to others. Unsupervised patients will often eat to the point that it causes serious physical harm or death. As a result, caregivers are often forced to place locks and alarms on refrigerators and pantries that contain food. Despite attempts to control the access to food, the typical adult patient with PWS is morbidly obese and, based on evaluation of published survival data, has an average life expectancy of 32 years of age. Unfortunately, neither dietary intervention nor currently available pharmaceutical therapies bring meaningful benefits to patients with PWS and, as a result, they experience severe and life-threatening consequences of their condition. Furthermore, existing surgical techniques such as bariatric surgery are contraindicated in PWS, as patients with PWS often overeat to a point whereby they can rupture their stomachs, which is frequently a cause of death in this patient population.

We have launched a co-sponsored four-year natural history study to advance understanding of the medical history of and medical events in people with PWS. PATH for PWS, is our natural history study conducted in collaboration with the Foundation for Prader-Willi Research, or FPWR, is independent of any specific development program and continues enrollment, with more than 400 of the 500-participant goal enrolled as of March 2019. The study is a non-interventional, observational study to evaluate occurrences of serious medical events in PWS, intended to inform development and clinical trial design for potential new treatments for PWS. The new ZGN-1258 findings do not impact the conduct of this study or our support of PATH for PWS.

Both ZGN-1061 and ZGN-1258 were discovered by our researchers as part of a multi-year campaign to identify highly potent and effective novel compounds with nonclinical safety profiles supportive of continued development. One core element of focus for optimization was to reduce or eliminate the potential for pro-thrombotic effects, a limiting factor that led to termination of development of our first-generation compound. To date, both new compounds have similar intrinsic potency against the MetAP2 enzyme and display appropriate activity in animal models of type 2 diabetes and obesity. We have observed degeneration and other anomalies in muscle tissue in rodent toxicology studies of ZGN-1258 as noted above. These effects were absent from other animal species in long term models and this finding has not been observed in any of our other MetAP2 inhibitors and appears to be specific to ZGN-1258.

In 2017, we also initiated development of a third, highly optimized MetAP2 development candidate, ZGN-1345, which is administered via the oral route and is targeted to the liver. During the fourth quarter of 2018 we announced that ZGN-1345 has been formally advanced to development candidate stage as a differentiated third asset within our pipeline. Nonclinical models have shown positive preliminary results in multiple liver disease indications. Further nonclinical studies are ongoing.

Populations of Interest

Type 2 Diabetes

According to the International Diabetes Federation, in 2017, 425 million adults (20 – 79 years old) worldwide were living with type 2 diabetes and that number is projected to increase to 693 million adults by 2045. In the United States alone, the Center for Disease Control estimated that there were 30 million adults living with diabetes and an estimated 84 million adults were pre-diabetic in 2017. Standard therapies for type 2 diabetes include physician recommended diet and exercise, oral hypoglycemic drugs such as biguanides, or metformin, through to a number of insulin options. Metformin is most often the first line pharmacotherapy for the treatment of type 2 diabetes primarily due to the extensive experience, low cost and favorable benefit risk associated with it. While metformin is likely to remain the initial treatment choice for patients with type 2 diabetes, these patients often progress to using additional treatments with oral anti-diabetes medications, such as sulfonylureas, DPP4 inhibitors or SGLT2 inhibitors as second line agents; injectable therapeutics, such as GLP-1 receptor agonists and insulin are often added as third and fourth line agents, along with various combination products. We expect that ZGN-1061, if approved, will compete within the type 2 diabetes injectable space with third line agents. It is estimated that 40-45% of patients with type 2 diabetes progress to needing insulin (estimated to be a $20.0 billion market) and that therapeutics have attained an 80% penetration rate into the diagnosed group of patients. The objective of each is to maintain a daily blood glucose level range recommended by the patient's physician, and to reach a therapeutic target of 7%, which is the U.S. goal (6.5% in Europe) glycated hemoglobin A1C, or A1C. Each of the current therapies alone has its limitations including numerous side effects. These side effects and the availability of a high number of treatment options, combined with the difficulty in daily management of glucose levels despite these treatments, creates a number of opportunities for a new third line agent to positively impact the unmet medical need.

We believe the diabetes drug market is estimated to be $35.0 billion and is on pace to grow to more than $71.0 billion by 2024. Pharmaceutical companies have been investigating new approaches to treating diabetes and market value has been maintained in the industry due to the introduction of these new products. We believe that ZGN-1061 MetAP2 inhibition serves the purpose of re-establishing balance to the ways the body stores and metabolizes fat and glucose. MetAP2 inhibitors

reduce the production of new fatty acid molecules by the liver and help convert stored fats into useful energy, while reducing hunger. In the setting of type 2 diabetes, these processes lead to improvement of glycemic control.

The following table summarizes the current pharmacological treatments for the treatment of type 2 diabetes:

Treatment	A1C Reduction	Key Advantages	Product Limitations
First line			
Biguanide (metformin)	1-1.5%	Inexpensive, safe, weight neutral/weight loss (up to 3 kg), rare hypoglycemia, extensive experience, reduction in CV events	Gastrointestinal effects, vitamin B12 deficiency, lactic acidosis
Second line			
Sulfonylurea (glimepiride, glipizide, glyburide)	1-1.5%	Inexpensive, extensive experience, reduction in CV events	Hypoglycemia, weight gain
GLP-1 Receptor Agonists (albiglutide, dulaglutide, exenatide, liraglutide, semaglutide)	1-1.5%	Weight loss (~1.5-3 kg), rare hypoglycemia, improvement in CV risk factors, improvement in CV mortality (liraglutide), improved postprandial glucose excursions	High cost, injection administration, gastrointestinal effects, risk of thyroid c-cell tumors, injection site reactions, acute pancreatitis risk, kidney injury risk
DPP-4 Inhibitors (alogliptin, linagliptin, saxagliptin, sitagliptin)	0.5-1%	Rare hypoglycemia, well tolerated	High cost, potential risk of acute pancreatitis, joint pain, potential congestive heart failure risk (saxagliptin, alogliptin)
SGLT-2 Inhibitors (canagliflozin, dapagliflozin, empagliflozin, ertugliflozin)	0.5-1.0%	Weight loss (0.1-4 kg), rare hypoglycemia, improvement in CV risk factors (empagliflozin and canagliflozin), improvement in CV mortality (empagliflozin)	High cost, genitourinary infections, hypotension, increase in LDL cholesterol, diabetic ketoacidosis, risk of amputation, bone fractures, and Fournier's gangrene
Thiazolidinediones (pioglitazone, rosiglitazone)	1-1.5%	Inexpensive, rare hypoglycemia, potential CV benefit (pioglitazone), benefit in NASH	Weight gain, edema/heart failure, bone fracture, bladder cancer (pioglitazone), increased LDL cholesterol
Insulins (under some circumstances may be first or second line)			
Regular and Rapid-Acting Insulins (aspart, glulisine, lispro, inhaled insulin)	Variable	Established standard of care and directly addresses insulin insufficiency	Mostly injection administration, hypoglycemia, weight gain, cough (inhaled insulin)
Intermediate-Acting Insulins (human NPH)	Variable	Established standard of care and directly addresses insulin insufficiency	Injection administration, hypoglycemia, weight gain
Long-Acting Insulins (glargine, detemir, degludec)	Variable	Established standard of care and directly addresses insulin insufficiency	Injection administration, hypoglycemia, weight gain

Treatment	A1C Reduction	Key Advantages	Product Limitations
Not included in ADA Primary Treatment Algorithm but may be used under specific circumstances			
Meglitinides (nateglinide, repaglinide)	0.5-1%	Improved postprandial glucose excursions	Hypoglycemia, weight gain
Alpha-Glucosidase Inhibitors (acarbose, miglitol)	0.5-1%	Weight loss, rare hypoglycemia, improved postprandial glucose excursions, nonsystemic	Modest efficacy, gastrointestinal effects
Dopamine-2 Agonist (bromocriptine)	0.5%	Rare hypoglycemia, may reduce risk of CV events	Modest efficacy, nausea, dizziness/syncope, hypotension, fatigue, somnolence
Amylin Mimetics (pramlintide)	0.5%	Weight loss, improved postprandial excursion	Injection administration, modest efficacy, gastrointestinal side effects, hypoglycemia under some conditions, for use with mealtime insulin only
Bile Acid Sequestrant (colesevelam)	0.5%	Rare hypoglycemia, decreased LDL cholesterol	Modest efficacy, gastrointestinal effects, increased triglycerides

Available combination products include: sulfonylurea/biguanide, biguanide/meglitinide, thiazolidinedione/sulfonylurea, thiazolidinedione/biguanide, DPP-4 inhibitor/biguanide, SGLT-2 inhibitor/biguanide, SGLT-2 inhibitor/DPP-4 inhibitor, long-acting insulin/GLP-1 receptor agonist

Data compiled from the American Diabetes Association, or ADA, Standards of Medical Care in Diabetes-2019: Pharmacologic Approaches to Glycemic Treatment, Diabetes Care 2019;42 (Supplement #1): S90–S102 and The Medical Letter on Drugs and Therapeutics: Drugs for Type 2 Diabetes, January 2017.

Prader-Willi Syndrome

PWS is the most common known genetic cause of life-threatening obesity. PWS is a rare and complex non-inherited genetic disorder, which results from abnormalities of the fifteenth chromosome. Symptoms associated with PWS are believed to result, in part, from a defect in the hypothalamus, an important supervisory center in the brain that controls many important bodily functions, such as hunger, metabolism of fats and carbohydrates, regulation of the sleep-wake cycle and expression of emotions.

Beginning in childhood, the brain of a patient with PWS fails to regulate metabolism and appetite normally. As a result, the vast majority of patients with PWS suffer from hyperphagia and obesity. Patients with PWS are constantly preoccupied with food and suffer from an unrelenting and overriding physiological drive to eat. Hyperphagia, a leading symptom of PWS, has a significant negative impact on the patients' quality of life and drives obesity and a range of associated co-morbidities. Normal satiety, or the feeling of fullness after eating, does not exist in a person with PWS. The physiological drive to eat is so powerful and overwhelming that most patients with PWS will go to great lengths to eat large quantities of food, even if it is spoiled, indigestible, or unpalatable to others. Furthermore, patients with PWS have a reduced propensity for nausea and vomiting. In addition to obesity, a variety of other symptoms can be associated with PWS, including cognitive challenges, intellectual disabilities, growth hormone deficiency/short stature, low sensitivity to pain, hypersomnolence, or excessive sleepiness, and infertility due to hypogonadism, or insufficient production of sex hormones.

Hyperphagia impairs a PWS patient's ability to live independently, requiring costly and constant supervision to prevent overeating. Without supervision, patients are likely to die prematurely as a result of choking, stomach rupture or tissue necrosis, or from complications caused by morbid obesity, such as heart failure or respiratory failure; in addition, preliminary data suggests that patients with PWS may be at a higher risk of death from pulmonary embolism than the general population.

Based on our evaluation of published survival data, the average life expectancy of patients with PWS is approximately 32 years of age. While a small number of patients with PWS are cared for in costly group homes, the majority of patients with PWS live in environments where caregivers often place locks and alarms on cabinets and refrigerators that contain food to impede a PWS patient's efforts to obtain food at all times. We estimate the typical annual cost of treating a patient with PWS is $100,000 to $200,000, excluding the often significant costs of drug therapies related to other medical and psychological conditions, and the costs of any lost time from work experienced by their families due to responsibilities related to the care of a patient with PWS.

Published population studies estimate that the prevalence of PWS in the United States and in the EU ranges from 1 in 8,000 to 1 in 50,000. PWS is diagnosed at an early age, typically in the first year of life. We believe that, due to the severity of the condition and its unique attributes, the vast majority of patients affected by PWS are therefore diagnosed. We believe that approximately 40-50% of patients with PWS are 12 years of age or older.

Although there are pharmacological treatments for various symptoms of PWS, such as replacement of human growth hormone in patients with PWS that are deficient in growth hormone, based on our discussions with physicians who treat patients with PWS, there are currently no effective pharmacological treatments for obesity and hyperphagia in PWS. For example, bariatric surgery, a type of weight-loss surgery, is contraindicated in patients with PWS due to poor outcomes related to an increased risk of rupture of the reduced stomach in the setting of sleeve gastrectomy or gastric bypass procedures, or rupture of the restricted esophagus in the setting of gastric banding procedures with the consequence of life-threatening gastric perforation. Apart from restricted access to food and constant supervision to prevent both life-threatening overeating and morbid obesity, there is currently no treatment for obesity and hyperphagia in patients with PWS.

Our Strategy

Our current strategy is to significantly improve the health and well-being of patients affected by both prevalent metabolic and rare diseases including type 2 diabetes, PWS and potentially other metabolically related disorders. Key elements of our strategy include:

- ***Advance the clinical development of MetAP2 inhibitors for the treatment of type 2 diabetes.*** We believe the patient population of type 2 diabetes would benefit from MetAP2 inhibitor treatment through concomitant improvements in glycemic control and body weight. These benefits were noted in our Phase 2 clinical trial of ZGN-1061, which studied the compound in patients with type 2 diabetes.
- ***Leverage the knowledge of our experienced team of drug developers that have deep expertise in the function of MetAP2 inhibitors and metabolic diseases.*** Our management team has deep expertise in type 2 diabetes, PWS, obesity and related metabolic diseases, the function of MetAP2 inhibitors, the strengths and weaknesses of current treatments for type 2 diabetes and obesity and the ability to recognize the potential of novel therapies for the treatment of type 2 diabetes and obesity. Our team is complemented by highly experienced external consultants and collaborators in the areas of drug discovery, development and regulatory approval. Based on our experience in MetAP2 inhibitor development, we are exploring new chemical approaches to identify new molecules targeting the liver for treatment of metabolic liver diseases such as non-alcoholic steatohepatitis, or NASH.
- ***Maintain flexibility in commercializing and maximizing the value of our research programs.*** While we intend to develop ZGN-1061 for indications such as type 2 diabetes and other metabolically related disorders, we may enter into strategic relationships with biotechnology or pharmaceutical companies to realize the full value of ZGN-1061. Additionally, we are evaluating ZGN-1061 for development in other indications. We intend to develop and commercialize ZGN-1258 in the United States (if our further evaluation of ZGN-1258 warrants continued development and commercialization) and other major market countries for PWS.

About ZGN-1061

ZGN-1061 was discovered by our researchers as part of a multi-year campaign to identify novel compounds that avoided limiting nonclinical safety concerns observed with our first-generation compound. The compound has similar potency and range of desired pharmacological activities in animal models as other MetAP2 inhibitors, including beloranib. Additionally, ZGN-1061 displays significantly improved safety margins in nonclinical studies, supporting the value of the compound as a more highly optimized drug product candidate.

ZGN-1061 acts through potent inhibition of MetAP2, an enzyme that modulates the activity of key cellular processes that control metabolism. MetAP2 inhibitors work, at least in part, by directing MetAP2 binding to cellular stress and growth factor mediators, thereby reducing the tone of signals that drive lipid synthesis by the liver and fat storage throughout the

body. In this manner, MetAP2 inhibition serves the purpose of re-establishing balance to the ways the body stores and metabolizes fat and glucose. MetAP2 inhibitors reduce the production of new fatty acid molecules by the liver and help convert stored fats into useful energy, while stimulating use of glucose and fats as an energy source. In the setting of type 2 diabetes, these processes lead to improvement of glycemic control.

During nonclinical development of ZGN-1061, we conducted research to understand the imbalance of thrombotic events observed in the course of beloranib clinical development. This research identified biomarkers associated with activation of blood clotting that subsequently were confirmed to be impacted in the setting of beloranib treatment in animals and cultured human endothelial cells. Further, beloranib was found to be retained in cultured endothelial cells, even after wash out, an effect that is related to the chemical structure of the compound. Modifying the side chain, as was done with ZGN-1061, leads to altered endothelial cell residence time and greatly reduces the ability of the compounds to impact endothelial cell replication, the display of pro-and anti-coagulant factors and the acceleration of clot formation, particularly following short-term exposure. Before committing ZGN-1061 to clinical development, the compound was evaluated for its potential to augment blood clotting in these same models and was found to be inactive with respect to thrombosis at doses greater than 90 times the anticipated clinical exposure.

About ZGN-1258

ZGN-1258 was also discovered by our researchers as part of a multi-year campaign to identify novel compounds that avoided limiting nonclinical safety concerns observed with our first-generation compound. The compound has similar potency and range of desired pharmacological activities in animal models as other MetAP2 inhibitors, including beloranib. ZGN-1258 displays significantly improved safety margins in nonclinical studies, supporting the value of the compound as a highly optimized drug product candidate. We have suspended our plans to file an IND for ZGN-1258 in order to evaluate ZGN-1258 following an unexpected finding in muscle tissue in rodent toxicology studies.

About ZGN-1345

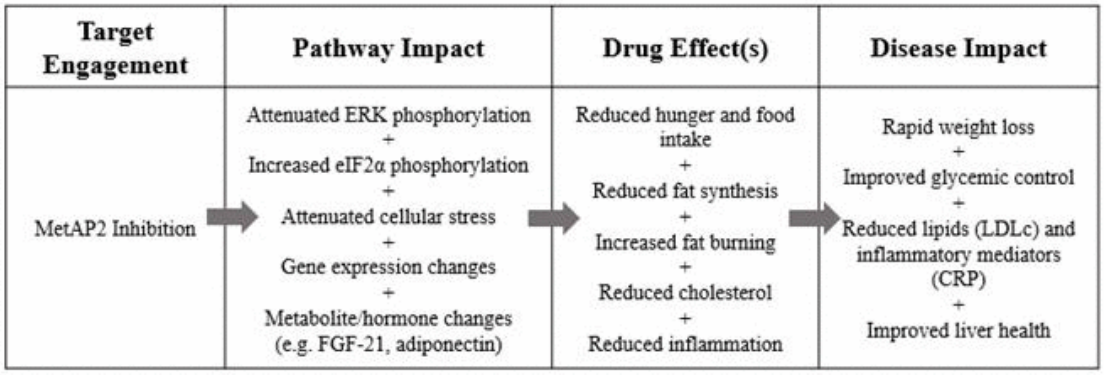
ZGN-1345 is our newly advanced early development candidate as a novel oral, liver-focused, MetAP2 inhibitor. In nonclinical studies, the compound has been shown to have a high degree of specificity of MetAP2 inhibition in the liver. High MetAP2 levels strongly correlate with more severe outcomes in advanced liver disease such as hepatocellular carcinoma. Additionally, nonclinical models have shown positive preliminary results in multiple liver disease indications, including NASH. Further nonclinical studies and early development activities are ongoing.

Mechanism of Action

First-generation MetAP2 inhibitors, such as beloranib, were evaluated for their potential for treating obesity following publication of studies in the Proceedings of the National Academy of Sciences in 2002 showing anti-obesity efficacy in animals treated with a prototype MetAP2 inhibitor. These studies showed that MetAP2 inhibitor treatment was associated with loss of fat tissue accompanied by an increase in fat oxidation, indicating a redirection of fuel usage toward utilization of stored fats as a source of energy. Reduced food intake was also observed in treated animals, suggesting either direct effects of the agent on central feeding regulation or activation of a feedback loop linking the release and oxidation of stored fat to appetite.

In 2004, the MetAP2 inhibitor fumagillin was shown to induce a novel protein-protein interaction involving MetAP2 and extracellular-signal-regulated kinase 1, or ERK1, a cell stress- and growth factor-stimulated kinase. This complex reduces the activation state of ERK1. A 2005 publication in *Diabetes* showed that animals lacking ERK1 resist both high fat diet-induced obesity and insulin resistance, supporting the hypothesis that attenuation of ERK activity could be an important component of the beneficial metabolic effects of MetAP2 inhibitor treatment. Additionally, several hormones well-documented to be involved in energy metabolism are affected by MetAP2 inhibitors, including leptin, adiponectin and fibroblast growth factor-21, or FGF-21. These hormones are thought to contribute to the weight-reducing effects of MetAP2 inhibitors like ZGN-1061, and also are known to be involved in control of body weight, fat metabolism and glucose metabolism. More recently, we have found that the MetAP2 may also interact with elongation initiation factor 2 alpha, or eIF2α, an important regulator of protein translation. Through this mechanism, we believe that MetAP2 inhibition may trigger a beneficial cell stress response that sequesters energy from fat stores, thus increasing tissue energy metabolism. This series of mechanistic effects leads to rapid and sustained reduction of excess body weight with ZGN-1061 treatment, such as has been observed in animal studies and our clinical trial experience to date.

An illustration of the MetAP2 inhibitor mechanism of action and therapeutic effects follows:



In the figure above, LDLc means low density lipoprotein and CRP means C-reactive protein.

Clinical Trials

Below is a summary of the Phase 1 clinical trial that was completed with ZGN-1061, and the Phase 2 clinical trial for which positive topline results were reported in January 2019.

Phase 1 Clinical Trial

The ZGN-1061 Phase 1 clinical trial, ZAF-1061-101, was a randomized, double-blind (subject, principal investigator and site staff), placebo-controlled trial consisting of a single ascending dose, or SAD, phase and a multiple ascending dose, or MAD, phase. The SAD phase was designed to assess effects of ZGN-1061 at six ascending dose levels relative to placebo in male or female healthy volunteers with a body mass index, or BMI, of 23 to <30 kg/m^2 (normal weight or overweight individuals). The MAD phase assessed effects of twice-weekly subcutaneous injections (eight doses in total) of ZGN-1061 over four weeks at three ascending dose levels relative to placebo, in male or female healthy volunteers with BMI 27-40 kg/m^2 (overweight or obese individuals). In addition to conventional safety and pharmacokinetic assessments, exploratory pharmacodynamic endpoints were also assessed. These measures were intended to provide a preliminary assessment of the potential of ZGN-1061 for weight management and inform the Phase 2 clinical trial design.

In this clinical trial, ZGN-1061 was rapidly absorbed and cleared with no evidence of pro-thrombotic effects. ZGN-1061 was well-tolerated, with no serious adverse events, or SAEs, and no severe adverse events, or AEs. There were no AEs leading to early withdrawal from the clinical trial. Treatment with ZGN-1061 resulted in improvements across multiple metabolic measures.

Phase 2 Clinical Trial

The ZGN-1061 Phase 2 clinical trial, ZAF-1061-201, is a randomized, double blinded, placebo-controlled evaluation of ZGN-1061 at 0.05 mg, 0.3 mg, 0.9 mg, and 1.8 mg or placebo administered subcutaneously every three days for 12 weeks in overweight or obese individuals with type 2 diabetes. The primary endpoints assessed safety and glycemic efficacy (HbA1c) for ZGN-1061 relative to placebo, and an array of secondary endpoints were included that investigated effects on supportive measures of glycemic efficacy, body weight and associated metabolic measures, exploratory biomarkers, pharmacokinetics, and patient reported outcomes. The trial was conducted through two sequential cohorts of evaluation. The first cohort included 129 individuals who were administered 0.05 mg, 0.3 mg, or 0.9 mg ZGN-1061 or placebo (1:1:1:1) and the second cohort included 46 participants who were administered 0.9 mg or 1.8 mg of ZGN-1061 or placebo (1:2:1). The clinical trial was conducted at 23 study sites in Australia and New Zealand.

Overall, all doses of ZGN-1061 were generally safe and well-tolerated, with an adverse event profile generally comparable to placebo. Adverse events were primarily mild or moderate in severity, with no noted trends by dose or type of AE reported. The most frequent treatment emergent AEs were injection site bruising, upper respiratory tract infection, and diarrhea; each of these categories of events occurred with relatively similar incidences to placebo. Three patients withdrew early due to an adverse event (injection site urticaria, 1.8 mg; upper abdominal pain, 0.9 mg; sensory disturbance, 0.05 mg).

Three patients (all 0.9 mg) reported serious AEs (upper abdominal pain, skin ulcer, anaphylactic reaction to antibiotic) and there were no deaths. There were no meaningful elevations in mean D-dimer concentrations, a robust and validated biomarker of blood clotting, across the dosing groups as compared to baseline or placebo and no CV safety signals observed. There were no meaningful changes among other clinical laboratory measures, vital signs, electrocardiograms, or measures pertaining to sleep latency (a common observation with our first-generation MetAP2 inhibitor) with ZGN-1061.

Treatment with ZGN-1061 demonstrated a statistically significant reduction in A1C for 0.9 mg and 1.8 mg versus placebo at Week 12 ($p=0.0003$ and $p<0.0001$, respectively), with a 1.1% reduction in A1C at the 1.8 mg dose relative to placebo. A1C levels continued to decline with no waning of effect for both doses through Week 12. Progressive weight reduction was also observed at the 1.8 mg dose ($p=0.0002$), with placebo-corrected weight loss of 2.3 kg (5.1 pounds) seen at Week 12 with no evidence of waning effect. Significant improvements were observed across multiple secondary efficacy endpoints and various relevant metabolic biomarkers, as well which will be presented at a later date as part of the full trial results.

Next Steps

We received a letter from the FDA in November 2018 placing a full clinical hold on the IND for the first U.S. clinical trial of ZGN-1061, our second-generation, investigational MetAP2 inhibitor currently in development for the treatment of type 2 diabetes. The FDA cited the possibility of CV safety risk based on our prior compound and outlined multiple potential paths for moving forward, including nonclinical or clinical options, to address these concerns in the ongoing development of ZGN-1061. We are assessing these options and a possible path forward and plan to request a Type A meeting with the FDA. The ex-U.S. Phase 1 and Phase 2 clinical trials of ZGN-1061 have been completed with no CV safety signals.

Nonclinical

ZGN-1061

We have conducted toxicology studies with ZGN-1061in support of clinical development. Based on the nonclinical assessment, ZGN-1061 is not genotoxic. Dose selection and precautions for our completed Phase 1 and Phase 2 clinical trials have been informed by nonclinical toxicology studies. Toxicological studies of up to nine months using intermittent dosing have established no observed adverse effect levels at higher exposures relative to the anticipated human doses. Embryofetal toxicity studies in multiple species have also been completed and suggest that there is a potential risk for the developing embryo or fetus to patients who are pregnant at exposure above that anticipated in the clinic; therefore, appropriate birth control and avoidance of pregnant persons within the clinical trial is mandatory.

ZGN-1258

We have initiated GLP toxicology studies to support filing an IND application with the FDA for ZGN-1258. However, in March 2019, we announced our decision to suspend plans to file an IND for ZGN-1258 in order to evaluate ZGN-1258 following an unexpected finding in muscle tissue in rodent toxicology studies.

ZGN-1345

We have conducted nonclinical studies with positive preliminary results in multiple liver disease indications with high unmet medical need and in toxicological screening. Further nonclinical studies are ongoing.

For information regarding amounts spent during each of the last three fiscal years on company-sponsored research and development activities, see Part II “Item 6—Selected Financial Data” of this Annual Report.

Manufacturing and Supply

ZGN-1061 is a small molecule drug that is chemically synthesized. The current process to produce ZGN-1061 drug product for Phase 2 clinical trials involves sterile filtration and lyophilization that is reconstituted prior to administration. The Phase 2 drug product was manufactured and released at our drug product contract manufacturing organization, or CMO. The manufacturing processes for both drug substance and drug product are under active development and optimization and are not yet validated for commercialization. We control our clinical trial supply chain by periodically meeting to assess clinical trial material needs and status of supply. The clinical supply forecast is managed internally by a cross functional working group and is used to aid in decision making for production planning.

ZGN-1258 is a small molecule drug that is chemically synthesized. The current process to produce ZGN-1258 for Phase 1 clinical trials involves synthesis of drug substance and production of sterile liquid drug product which can be stored frozen. The Phase 2 drug product will be developed as a sterile, lyophilized product for reconstitution prior to administration, if further evaluation warrants continued development.

We currently have no manufacturing facilities and limited personnel with manufacturing experience. We rely on contract manufacturers to produce both drug substance and drug product required for our clinical trials. Any delays encountered with manufacturing activities, CMO scheduling or raw material supply could delay the manufacturing of finished drug product. No long-term supply agreements are in place with our contractors, and each batch is individually contracted under a work order, which is governed by a quality agreement. We plan to continue to rely upon contract manufacturers and, potentially, collaboration partners to manufacture commercial quantities of ZGN-1061, ZGN-1258 and ZGN-1345, if approved, or if we elect to commercialize these product candidates on our own. Our current scale of manufacturing is adequate to support all of our current needs for clinical trial supplies. For commercial quantities for larger populations, we will need to identify contract manufacturers or partners to produce ZGN-1061 on a larger scale.

Sales and Marketing

Based on our early stage of development, we have not yet established commercial organization or distribution capabilities, nor have we entered into any partnership or co-promotion arrangements with an established pharmaceutical or biotechnology company. To develop the appropriate commercial infrastructure to launch our product candidates, we may either do so on our own or by establishing alliances with one or more pharmaceutical or other biotechnology company collaborators, depending on, among other things, the applicable indications, the related development costs and our available resources.

Licenses

CKD License

In July 2009, we entered into an Exclusive License Agreement with Chong Kun Dang Pharmaceutical Corp. of South Korea, or CKD, pursuant to which we exclusively licensed beloranib from CKD on a worldwide basis, with the exception of South Korea. In consideration of such exclusive license, we paid an initial license fee to CKD, paid a one-time fee following initiation of a proof of concept trial, agreed to make milestone payments of up to $30.0 million (of which $7.5 million has been paid, including $3.3 million that was paid in the form of our common stock (valued at $3.6 million) as a result of an amendment to our license agreement and entry into a subscription agreement with CKD) to CKD upon the achievement of certain specified events, and agreed to pay a portion of sublicensing income to CKD. Furthermore, if we receive marketing approval for beloranib, we will pay single-digit royalties to CKD based on annual net sales of beloranib on a country-by-country and product-by-product basis until the later to occur of (i) the expiration of the last to expire patent in such country within the CKD patent rights containing a valid claim covering beloranib or its use for which regulatory approval has been obtained in such country, or (ii) ten years from the first commercial sale of beloranib in such country. Pursuant to this agreement, we committed to using commercially reasonable efforts to develop and commercialize beloranib. This agreement will remain in effect on a country-by-country and product-by-product basis until royalties are no longer due in such country, subject to earlier termination by either party upon mutual consent, or in the event of uncured breach or insolvency on the part of the other party, or by us for any reason up to 60 days' prior notice.

Children's License

In January 2007, we entered into an Exclusive License Agreement with Children's Medical Center Corporation, or Children's, pursuant to which we exclusively licensed certain patent rights from Children's on a worldwide basis. The licensed patent rights relate to decreasing the growth of fat tissue, and thereby cover the use of ZGN-1061 and related molecules as anti-obesity agents. In consideration of such exclusive license, we paid an initial license fee upon execution of the license to Children's and annual maintenance fees through the fifth anniversary of the date of the license. We also agreed to make milestone payments to Children's of up to $2.7 million (of which $0.4 million has been paid) with respect to the first licensed product and up to $1.3 million with respect to each subsequent licensed product, if any, that is a new chemical entity upon the achievement of certain specified events and to pay a portion of sublicensing income to Children's. If we receive marketing approval for ZGN-1061, we will pay single-digit royalties to Children's based on net sales of ZGN-1061 until the later to occur of (i) the expiration of the last to expire patent in such country within the licensed patents containing a valid claim covering ZGN-1061 or (ii) 15 years from the date of the agreement. This agreement will remain in effect for the longer of (i) 15 years or (ii) the life of the last expiring licensed patent, subject to earlier termination (x) by Children's in the event

of our insolvency or our failure to cure a breach within 60 days (30 days in the case of non-payment) of receiving written notice thereof, or (y) by us for any reason upon 120 days' prior written notice.

Intellectual Property

We strive to protect and enhance the proprietary technologies that we believe are important to our business, including seeking and maintaining patents intended to cover our products and compositions, their methods of use and any other inventions that are important to the development of our business. We also rely on trade secrets to protect aspects of our business that are not amenable to, or that we do not consider appropriate for, patent protection.

Our success will depend significantly on our ability to obtain and maintain patent and other proprietary protection for commercially important technology, inventions and know-how related to our business, defend and enforce our patents, preserve the confidentiality of our trade secrets and operate without infringing the valid and enforceable patents and proprietary rights of third parties. We also rely on know-how, continuing technological innovation and in-licensing opportunities to develop, strengthen and maintain the proprietary position of ZGN-1061 and our other development programs.

As of March 1, 2019, we own two issued U.S. patents, two pending U.S. patent applications and related pending foreign counterpart patent applications, as well as one pending Patent Cooperation Treaty, or PCT patent application, and three pending U.S. provisional patent applications that relate to ZGN-1061.

As of March 1, 2019, we own one issued U.S. patent, two pending U.S. patent applications, and one pending provisional patent application and related worldwide patent application, that relate to ZGN-1258.

As of March 1, 2019, we own two pending U.S. patent applications, and related worldwide patent applications, and two pending PCT patent applications that relate to ZGN-1345.

As of March 1, 2019, we own twenty-one issued U.S. patents, and three pending U.S. patent applications with pending foreign counterpart applications and three pending U.S. provisional patent applications, all of which relate to our internal efforts to discover novel MetAP2 inhibitors.

The term of individual patents depends upon the legal term of the patents in the countries in which they are obtained. In most countries in which we file, the patent term is 20 years from the date of filing the non-provisional application. In the United States, a patent's term may be lengthened by patent term adjustment, which compensates a patentee for administrative delays by the U.S. Patent and Trademark Office, or U.S. PTO, in granting a patent, or may be shortened if a patent is terminally disclaimed over an earlier-filed patent. In addition, in certain instances, a patent term can be extended to recapture a portion of the term effectively lost as a result of the FDA regulatory review period. However, the restoration period cannot be longer than five years and the total patent term including the restoration period must not exceed 14 years following FDA approval. The duration of foreign patents varies in accordance with provisions of applicable local law, but typically is also twenty years from the earliest effective filing date. Our issued patents will expire on dates ranging from 2020 to 2036. However, the actual protection afforded by a patent varies on a claim by claim and country to country basis for each applicable product and depends upon many factors, including the type of patent, the scope of its coverage, the availability of regulatory related extensions, the availability of legal remedies in a particular country and the validity and enforceability of the patent.

Furthermore, the patent positions of biotechnology and pharmaceutical products and processes like those we intend to develop and commercialize are generally uncertain and involve complex legal and factual questions. No consistent policy regarding the breadth of claims allowed in such patents has emerged to date in the United States. The patent situation outside the United States is even more uncertain. Changes in either the patent laws or in interpretations of patent laws in the United States and other countries can diminish our ability to protect our inventions, and enforce our intellectual property rights and more generally, could affect the value of intellectual property. Accordingly, we cannot predict the breadth of claims that may be allowed or enforced in our patents or in third-party patents.

The biotechnology and pharmaceutical industries are characterized by extensive litigation regarding patents and other intellectual property rights. Our ability to maintain and solidify our proprietary position for our drugs and technology will depend on our success in obtaining effective claims and enforcing those claims once granted. We do not know whether any of the patent applications that we may file or license from third parties will result in the issuance of any patents. The issued patents that we own or may receive in the future, may be challenged, invalidated or circumvented, and the rights granted under any issued patents may not provide us with proprietary protection or competitive advantages against competitors with

similar technology. Furthermore, our competitors may be able to independently develop and commercialize similar drugs or duplicate our technology, business model or strategy without infringing our patents. Because of the extensive time required for clinical development and regulatory review of a drug we may develop, it is possible that, before any of our drugs can be commercialized, any related patent may expire or remain in force for only a short period following commercialization, thereby reducing any advantage of any such patent.

As a result of the America Invents Act of 2011, the United States transitioned to a first-inventor-to-file system in March 2013, under which, assuming the other requirements for patentability are met, the first inventor to file a patent application will be entitled to the patent. This will require us to minimize the time from invention to the filing of a patent application.

We may rely, in some circumstances, on trade secrets and unpatented know-how to protect our technology. However, trade secrets can be difficult to protect. We seek to protect our proprietary technology and processes, in part, by entering into confidentiality agreements with our consultants, scientific advisors and contractors and invention assignment agreements with our employees. We also seek to preserve the integrity and confidentiality of our data and trade secrets by maintaining physical security of our premises and physical and electronic security of our information technology systems. While we have confidence in these individuals, organizations and systems, agreements or security measures may be breached and we may not have adequate remedies for any breach. In addition, our trade secrets may otherwise become known or be independently discovered by competitors. To the extent that our consultants, contractors or collaborators use intellectual property owned by others in their work for us, disputes may arise as to the rights in related or resulting know-how and inventions. For more information, see "Risk Factors—Risks Related to our Intellectual Property."

Our commercial success will also depend in part on not infringing the proprietary rights of third parties. It is uncertain whether the issuance of any third-party patent would require us to alter our development or commercial strategies, or our drugs or processes, obtain licenses or cease certain activities. Our breach of any license agreements or failure to obtain a license to proprietary rights that we may require to develop or commercialize our future drugs may have a material adverse impact on us. If third parties prepare and file patent applications in the United States that also claim technology to which we have rights, we may have to participate in interference proceedings in the U.S. PTO, to determine priority of invention.

In addition, substantial scientific and commercial research has been conducted for many years in the areas in which we have focused our development efforts, which has resulted in third parties having a number of issued patents and pending patent applications. Patent applications in the United States and elsewhere are published only after 18 months from the priority date. The publication of discoveries in the scientific or patent literature frequently occurs substantially later than the date on which the underlying discoveries were made. Therefore, patent applications relating to drugs similar to ZGN-1061, ZGN-1258, ZGN-1345 and any future drugs, discoveries or technologies we might develop may have already been filed by others without our knowledge.

Competition

The biopharmaceuticals industry is highly competitive. There are many public and private biopharmaceutical companies, universities, governmental agencies and other research organizations actively engaged in the research and development of products that may be similar to our product candidates or address similar markets. It is probable that the number of companies seeking to develop products and therapies similar to our products will increase. Many of these and other existing or potential competitors have substantially greater financial, technical and human resources than we do and may be better equipped to develop, manufacture and market products. These competitors may develop and introduce products and processes comparable or superior to ours.

Existing Type 2 Diabetes Drugs

Biguanides, or metformin, is first line pharmacotherapy for the treatment of type 2 diabetes primarily due to the extensive experience, low cost and favorable benefit risk associated with it. While metformin is likely to remain the initial choice for the treatment of type 2 diabetes, ZGN-1061 will compete with sulfonylureas, GLP-1 receptor agonists, DPP4 inhibitors, SGLT2 inhibitors, thiazoladinediones, insulin, and various combination products. Although these pharmacotherapies are all effective to some extent in the treatment of type 2 diabetes, they each have notable limitations, and have not been found to halt the progression of type 2 diabetes. Therefore, additional effective and durable options are needed.

There are a number of pharmaceutical and biotechnology companies with type 2 diabetes drugs that are pursuing products with unique mechanisms of action for the treatment of type 2 diabetes.

PWS Drugs

There are no current pharmacological treatments for regulating hunger and hyperphagia-related behaviors of patients with PWS, and bariatric surgery is contraindicated in patients with PWS. Multiple products are currently under investigation for treatment of hyperphagia and/or obesity in individuals with PWS including assessment of diazoxide choline controlled-release for treatment of hyperphagia by Soleno Therapeutics, Inc., intranasal carbetocin for treatment of hyperphagia by Levo Therapeutics Inc., livoletide for the treatment of hyperphagia by Millendo Therapeutics, Inc. and liraglutide for weight management by Novo Nordisk. These four investigational products are either under Phase 3 assessment or are preparing for Phase 3 assessment. Several products are being explored in various stages of Phase 1 and Phase 2 of development. No products under investigation by other companies are MetAP2 inhibitors and the safety and efficacy of their product candidates have not yet been established.

Government Regulation

Government authorities in the United States at the federal, state and local level and in other countries extensively regulate, among other things, the research, development, testing, manufacture, quality control, approval, labeling, packaging, storage, record-keeping, promotion, advertising, distribution, post-approval monitoring and reporting, marketing and export and import of drug products such as ZGN-1061, ZGN-1258 and ZGN-1345. Generally, before a new drug can be marketed, considerable data demonstrating its quality, safety and efficacy must be obtained, organized into a format specific to each regulatory authority, submitted for review and approved by such regulatory authority.

U.S. Drug Development

In the United States, the FDA regulates drugs under the Federal Food, Drug, and Cosmetic Act, or FDCA, and applicable regulations. Drugs are also subject to other federal, state and local statutes and regulations. The process of obtaining regulatory approvals and the subsequent compliance with appropriate federal, state, local and foreign statutes and regulations require the expenditure of substantial time and financial resources. Failure to comply with the applicable U.S. requirements at any time during the product development process, approval process or after approval, may subject an applicant to administrative or judicial sanctions. These sanctions could include, among other actions, the FDA's refusal to approve pending applications, withdrawal of an approval, a clinical hold, untitled or warning letters, voluntary product recalls, withdrawals from the market, product seizures, total or partial suspension of production or distribution injunctions, fines, refusals of government contracts, restitution, disgorgement, or civil or criminal penalties. Any agency or judicial enforcement action could have a material adverse effect on us.

Our product candidates must be approved by the FDA through the New Drug Application, or NDA, process before they may be legally marketed in the United States. The process required by the FDA before a drug may be marketed in the United States generally involves the following:

- Completion of extensive nonclinical, sometimes referred to as nonclinical laboratory tests, animal studies and formulation studies in accordance with applicable regulations, including the FDA's Good Laboratory Practice, or GLP, regulations;
- Submission to the FDA of an IND, which must become effective before human clinical trials may begin in the United States;
- Performance of adequate and well-controlled human clinical trials in accordance with applicable IND and other clinical trial-related regulations, sometimes referred to as good clinical practices, or GCPs, to establish the safety and efficacy of the proposed drug for its proposed indication;
- Submission to the FDA of an NDA for a new drug;
- A determination by the FDA within 60 days of its receipt of an NDA to file the NDA for review;
- Satisfactory completion of an FDA pre-approval inspection of the manufacturing facility or facilities where the drug is produced to assess compliance with the FDA's current good manufacturing practice, or cGMP, requirements to assure that the facilities, methods and controls are adequate to preserve the drug's identity, strength, quality and purity;
- Potential FDA audit of the nonclinical study and/or clinical trial sites that generated the data in support of the NDA; and
- FDA review and approval of the NDA prior to any commercial marketing or sale of the drug in the United States.

The data required to support an NDA is generated in two distinct development stages: nonclinical and clinical. For new chemical entities, the nonclinical development stage generally involves synthesizing the active component, developing the formulation and determining the manufacturing process, as well as carrying out non-human toxicology, pharmacology and drug metabolism studies in the laboratory, which support subsequent clinical testing. The conduct of the nonclinical tests must comply with federal regulations, including GLPs. The sponsor must submit the results of the nonclinical tests, together with manufacturing information, analytical data, any available clinical data or literature and a proposed clinical protocol, to the FDA as part of the IND. An IND is a request for authorization from the FDA to administer an investigational drug product to humans in the United States. The IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA raises concerns or questions regarding the proposed clinical trials and places the IND on clinical hold within that 30-day time period. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. The FDA may also impose clinical holds on a drug candidate at any time before or during clinical trials due to safety concerns or non-compliance. Accordingly, we cannot be sure that submission of an IND will result in the FDA allowing clinical trials to begin, or that, once begun, issues will not arise that could cause the clinical trial to be suspended or terminated.

The clinical stage of development involves the administration of the drug candidate to healthy volunteers or patients under the supervision of qualified investigators, generally physicians not employed by or under the clinical trial sponsor's control, in accordance with GCPs, which include the requirement that all research subjects provide their informed consent for their participation in any clinical trial. Clinical trials are conducted under protocols detailing, among other things, the objectives of the clinical trial, dosing procedures, subject selection and exclusion criteria, and the parameters to be used to monitor subject safety and assess efficacy. Each protocol, and any subsequent amendments to the protocol, must be submitted to the FDA as part of the IND. Further, each clinical trial must be reviewed and approved by an independent institutional review board, or IRB, at or servicing each institution at which the clinical trial will be conducted. An IRB is charged with protecting the welfare and rights of clinical trial participants and considers such items as whether the risks to individuals participating in the clinical trials are minimized and are reasonable in relation to anticipated benefits. The IRB also approves the informed consent form that must be provided to each clinical trial subject or his or her legal representative and must monitor the clinical trial until completed. There are also requirements governing the reporting of ongoing clinical trials and completed clinical trial results to public registries.

Clinical trials are generally conducted in three sequential phases that may overlap, known as Phase 1, Phase 2 and Phase 3 clinical trials. Phase 1 clinical trials generally involve a small number of healthy volunteers who are initially exposed to a single dose and then multiple doses of the product candidate. The primary purpose of these clinical trials is to assess the metabolism, pharmacologic action, side effect tolerability and safety of the drug. Phase 2 clinical trials typically involve studies in disease-affected patients to determine the dose required to produce the desired benefits. At the same time, safety and further pharmacokinetic and pharmacodynamic information is collected, as well as identification of possible adverse effects and safety risks and preliminary evaluation of efficacy. Phase 3 clinical trials generally involve large numbers of patients at multiple sites, in multiple countries (from several hundred to several thousand subjects) and are designed to provide the data necessary to demonstrate the efficacy of the product for its intended use, its safety in use, and to establish the overall benefit/risk relationship of the product and provide an adequate basis for physician labeling. Phase 3 clinical trials may include comparisons with placebo and/or other comparator treatments. The duration of treatment is often extended to mimic the actual use of a product during marketing. Generally, two adequate and well-controlled Phase 3 clinical trials are required by the FDA for approval of an NDA, although additional Phase 3 clinical trials may be required for certain indications.

Post-approval trials, sometimes referred to as Phase 4 clinical trials, may be conducted after initial marketing approval. These clinical trials are used to gain additional experience from the treatment of patients in the intended therapeutic indication. In certain instances, the FDA may mandate the performance of Phase 4 clinical trials.

Progress reports detailing the results of the clinical trials conducted under an IND must be submitted at least annually to the FDA. Within 15 calendar days after the sponsor determines that the information qualifies for reporting, written IND safety reports must be submitted to the FDA and the investigators for serious and unexpected suspected adverse events, findings from animal or in vitro testing or other studies that suggest a significant risk for human subjects and any clinically important increase in the rate of a serious suspected adverse reaction over that listed in the protocol or investigator brochure. The sponsor also must notify the FDA of any unexpected fatal or life-threatening suspected adverse reaction within seven calendar days after the sponsor's initial receipt of the information. Phase 1, Phase 2 and Phase 3 clinical trials may not be completed successfully within any specified period, if at all. The FDA, the IRB, or the sponsor may suspend or terminate a clinical trial at any time on various grounds, including a finding that the research subjects or patients are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution if the clinical trial is not being conducted in accordance with the IRB's requirements or if the drug has been associated with unexpected

serious harm to patients. Additionally, some clinical trials are overseen by an independent group of qualified experts organized by the clinical trial sponsor, known as a data safety monitoring board or committee. This group provides authorization for whether or not a clinical trial may move forward at designated check points based on access to certain data from the clinical trial. We may also suspend or terminate a clinical trial based on evolving business objectives and/or competitive climate. Concurrent with clinical trials, companies usually complete additional animal studies and must also develop additional information about the chemistry and physical characteristics of the drug as well as finalize a process for manufacturing the product in commercial quantities in accordance with cGMP requirements. The manufacturing process must be capable of consistently producing quality batches of the drug candidate and manufacturers, among other things, must develop methods for testing the identity, strength, quality and purity of the final drug product. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to demonstrate that the drug candidate does not undergo unacceptable deterioration over its shelf life.

NDA and FDA Review Process

Following clinical trial completion, clinical trial data are analyzed to assess safety and efficacy. The results of nonclinical studies and clinical trials are then submitted to the FDA as part of an NDA, along with proposed labeling for the product and information about the manufacturing process and facilities that will be used to ensure product quality, results of analytical testing conducted on the chemistry of the drug, and other relevant information. The NDA is a request for approval to market the drug and must contain proof of safety and efficacy, which is demonstrated by extensive nonclinical and clinical testing. The application includes both negative or ambiguous results of nonclinical studies and clinical trials as well as positive findings. Data may come from company-sponsored clinical trials intended to test the safety and efficacy of a use of a product, or from a number of alternative sources, including studies initiated by investigators. To support marketing approval, the data submitted must be sufficient in quality and quantity to establish the safety and efficacy of the investigational drug product to the satisfaction of the FDA. The submission of an NDA is subject to the payment of substantial user fees; a waiver of such fees may be obtained under certain limited circumstances. FDA approval of an NDA must be obtained before a drug may be offered for sale in the United States.

Under the Prescription Drug User Fee Act, or PDUFA, as amended, each NDA must be accompanied by a user fee. The FDA adjusts the PDUFA user fees on an annual basis. According to the FDA's fee schedule for fiscal year 2019, the user fee for an application requiring clinical data, such as an NDA, is $2,588,478. PDUFA also imposes an annual prescription drug product program fee for human drugs of $309,915. Fee waivers or reductions are available in certain circumstances, including a waiver of the application fee for the first application filed by a small business. Additionally, no user fees are assessed on NDAs for products designated as orphan drugs, unless the product also includes a non-orphan indication.

The FDA reviews all NDAs submitted before it accepts them for filing and may request additional information rather than accepting an NDA for filing. The FDA must make a decision on accepting an NDA for filing within 60 days of receipt. Once the submission is accepted for filing, the FDA begins an in-depth review of the NDA. Under the goals and policies agreed to by the FDA under PDUFA, the FDA has 10 months from the filing date in which to complete its initial review of a standard new molecular-entity NDA and respond to the applicant, and six months from the filing date for a priority new molecular-entity NDA. The FDA does not always meet its PDUFA goal dates for standard and priority NDAs, and the review process is often significantly extended by FDA requests for additional information or clarification.

After the NDA submission is accepted for filing, the FDA reviews the NDA to determine, among other things, whether the proposed product is safe and effective for its intended use, and whether the product is being manufactured in accordance with cGMP to assure and preserve the product's identity, strength, quality and purity. The FDA may refer applications for novel drug products or drug products which present difficult questions of safety or efficacy to an advisory committee, typically a panel that includes clinicians and other experts, for review, evaluation and a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions. The FDA will likely re-analyze the clinical trial data, which could result in extensive discussions between the FDA and us during the review process. The review and evaluation of an NDA by the FDA is extensive and time consuming and may take longer than originally planned to complete, and we may not receive a timely approval, if at all.

Before approving an NDA, the FDA will conduct a pre-approval inspection of the manufacturing facilities for the new product to determine whether they comply with cGMPs. The FDA will not approve the product 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. In addition, before approving an NDA, the FDA may also audit data from clinical trials to ensure compliance with GCP requirements. After the FDA evaluates the application, manufacturing process and manufacturing facilities, it may issue an approval letter or a Complete Response Letter. An approval letter

authorizes commercial marketing of the drug with specific prescribing information for specific indications. A Complete Response Letter indicates that the review cycle of the application is complete and the application is not ready for approval. A Complete Response Letter usually describes all of the specific deficiencies in the NDA identified by the FDA. The Complete Response Letter may require additional clinical data and/or an additional pivotal Phase 3 clinical trial(s), and/or other significant and time-consuming requirements related to clinical trials, nonclinical studies or manufacturing. If a Complete Response Letter is issued, the applicant may either resubmit the NDA, addressing all of the deficiencies identified in the letter, withdraw the application, or request an opportunity for a hearing. Even if such data and information is submitted, the FDA may ultimately decide that the NDA does not satisfy the criteria for approval. Data obtained from clinical trials are not always conclusive and the FDA may interpret data differently than we interpret the same data.

There is no assurance that the FDA will ultimately approve a drug product for marketing in the United States and we may encounter significant difficulties or costs during the review process. If a product receives marketing approval, the approval may be significantly limited to specific diseases and dosages or the indications for use may otherwise be limited, which could restrict the commercial value of the product. Further, the FDA may require that certain contraindications, warnings or precautions be included in the product labeling or may condition the approval of the NDA on other changes to the proposed labeling, development of adequate controls and specifications, or a commitment to conduct post-market testing or clinical trials and surveillance to monitor the effects of approved products. For example, the FDA may require Phase 4 testing which involves clinical trials designed to further assess drug safety and effectiveness and may require testing and surveillance programs to monitor the safety of approved products that have been commercialized. The FDA may also place other conditions on approvals including the requirement for a Risk Evaluation and Mitigation Strategy, or REMS, to assure the safe use of the drug. If the FDA concludes a REMS is needed, the sponsor of the NDA must submit a proposed REMS. The FDA will not approve the NDA without an approved REMS, if required. A REMS 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. Any of these limitations on approval or marketing could restrict the commercial promotion, distribution, prescription or dispensing of products. Product approvals may be withdrawn for non-compliance with regulatory standards or if problems occur following initial marketing.

Orphan Drug Designation

Under the Orphan Drug Act, the FDA may grant orphan designation to a drug or biological product intended to treat a rare disease or condition, which is generally a disease or condition that affects fewer than 200,000 individuals in the United States, or more than 200,000 individuals in the United States and for which there is no reasonable expectation that the cost of developing and making a drug or biological product available in the United States for this type of disease or condition will be recovered from sales of the product. Orphan product designation must be requested before submitting an NDA. After the FDA grants orphan product designation, the identity of the therapeutic agent and its potential orphan use are disclosed publicly by the FDA. Orphan product designation does not convey any advantage in or shorten the duration of the regulatory review and approval process.

If a product that has orphan designation subsequently receives the first FDA approval for the disease or condition for which it has such designation, the product is entitled to orphan product exclusivity, which means that the FDA may not approve any other applications to market the same drug or biological product for the same indication for seven years, except in limited circumstances, such as a showing of clinical superiority to the product with orphan exclusivity. Competitors, however, may receive approval of different products for the indication for which the orphan product has exclusivity or obtain approval for the same product but for a different indication for which the orphan product has exclusivity. Orphan product exclusivity also could block the approval of one of our products for seven years if a competitor obtains approval of the same drug product as defined by the FDA or if our product candidate is determined to be contained within the competitor's product for the same indication or disease. If a drug or biological product designated as an orphan product receives marketing approval for an indication broader than what is designated, it may not be entitled to orphan product exclusivity. Orphan drug status in the EU has similar, but not identical, benefits.

Expedited Development and Review Programs

The FDA has a Fast Track program that is intended to expedite or facilitate the process for reviewing new drugs and biological products that are intended to treat a serious or life-threatening condition and demonstrate the potential to address unmet medical needs for the condition. Fast Track designation applies to the combination of the product and the specific indication for which it is being studied. The sponsor of a new drug or biologic may request the FDA to designate the drug or biologic as a Fast Track product at any time during the clinical development of the product. Unique to a Fast Track product, the FDA may consider for review sections of the marketing application on a rolling basis before the complete application is submitted, if the sponsor provides a schedule for the submission of the sections of the application, the FDA agrees to accept sections of the application and determines that the schedule is acceptable, and the sponsor pays any required user fees upon submission of the first section of the application.

Any product submitted to the FDA for marketing, including under a Fast Track program, may be eligible for other types of FDA programs intended to expedite development and review, such as priority review and accelerated approval.

Any product is eligible for priority review if it treats a serious or life-threatening condition and, if approved, would provide a significant improvement in safety and effectiveness compared to available therapies. The FDA will attempt to direct additional resources to the evaluation of an application for a new drug or biologic designated for priority review in an effort to facilitate the review.

Drug or biological products studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit over existing treatments may receive accelerated approval, which means that they may be approved on the basis of adequate and well-controlled clinical trials establishing that the product has an effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit, or on the basis of an effect on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, or IMM, that is reasonably likely to predict an effect on IMM or other clinical benefit. As a condition of approval, the FDA may require that a sponsor of a drug or biological product receiving accelerated approval perform adequate and well-controlled post-marketing clinical trials. If the FDA concludes that a drug shown to be effective can be safely used only if distribution or use is restricted, it will require such post-marketing restrictions as it deems necessary to assure safe use of the drug, such as:

- distribution restricted to certain facilities or physicians with special training or experience; or
- distribution conditioned on the performance of specified medical procedures.

The limitations imposed would be commensurate with the specific safety concerns presented by the drug. In addition, the FDA currently requires as a condition for accelerated approval, pre-approval of promotional materials, which could adversely impact the timing of the commercial launch of the product.

Additionally, a drug or biological product may be eligible for designation as a Breakthrough Therapy if the product is intended, alone or in combination with one or more other drugs or biologics, to treat a serious or life-threatening condition and preliminary clinical evidence indicates that the product may demonstrate substantial improvement over currently approved therapies on one or more clinically significant endpoint. The benefits of Breakthrough Therapy designation include the same benefits as Fast Track designation, plus intensive guidance from the FDA to ensure an efficient drug development program. Fast Track designation, priority review, accelerated approval and Breakthrough Therapy designation do not change the standards for approval but may expedite the development or approval process.

Pediatric Clinical Trials

Under the Pediatric Research Equity Act, or PREA, as amended, an NDA or supplement to an NDA must contain data to assess the safety and efficacy of the drug for the claimed indications in all relevant pediatric subpopulations and to support dosing and administration for each pediatric subpopulation for which the product is safe and effective. The FDA may grant deferrals for submission of data or full or partial waivers.

The FDCA requires that a sponsor who is planning to submit a marketing application for a drug or biological product that includes a new active ingredient, new indication, new dosage form, new dosing regimen or new route of administration submit an initial Pediatric Study Plan, or PSP, within sixty days of an end-of-Phase 2 meeting or as may be agreed between the sponsor and the FDA. The initial PSP must include an outline of the pediatric study or studies that the sponsor plans to conduct, including study objectives and design, age groups, relevant endpoints and statistical approach, or a justification for not including such detailed information, and any request for a deferral of pediatric assessments or a full or partial waiver of the requirement to provide data from pediatric studies along with supporting information. The FDA and the sponsor must reach agreement on the PSP. A sponsor can submit amendments to an agreed-upon initial PSP at any time if changes to the pediatric plan need to be considered based on data collected from nonclinical studies, early phase clinical trials, and/or other clinical development programs.

Post-Marketing Requirements

Following approval of a new product, a pharmaceutical or biotechnology company and the approved product are subject to continuing regulation by the FDA, including, among other things, monitoring and recordkeeping activities, reporting to the applicable regulatory authorities of adverse experiences with the product, providing the regulatory authorities with updated safety and efficacy information, product sampling and distribution requirements, and complying with promotion and advertising requirements, which include, among others, standards for direct-to-consumer advertising, restrictions on

promoting drugs for uses or in patient populations that are not described in the drug's approved labeling (known as "off-label use"), and requirements for promotional activities involving the internet. The FDA also imposes limitations on industry-sponsored scientific and educational activities. Although physicians may prescribe legally available drugs for off-label uses, manufacturers may not market or promote such off-label uses. Prescription drug promotional materials must be submitted to the FDA in conjunction with their first use. Modifications or enhancements to the product or its labeling or changes of the site of manufacture are often subject to the approval of the FDA and other regulators, which may or may not be received or may result in a lengthy review process.

Any distribution of prescription drug products and pharmaceutical samples must comply with the U.S. Prescription Drug Marketing Act, or the PDMA, a part of the FDCA.

In the United States, once a product is approved, its manufacture is subject to comprehensive and continuing regulation by the FDA. The FDA regulations require that products be manufactured in specific facilities, which are inspected as part of the FDA's review of the NDA, and in accordance with cGMP. We rely, and expect to continue to rely, on third parties for the production of clinical and commercial quantities of our products in accordance with cGMP regulations. cGMP regulations require among other things, quality control and quality assurance as well as the corresponding maintenance of records and documentation and the obligation to investigate and correct any deviations from cGMP. Drug manufacturers and other entities involved in the manufacture and distribution of approved drugs 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 and other laws. Accordingly, manufacturers must continue to expend time, money, and effort in the area of production and quality control to maintain cGMP compliance. These regulations also impose certain organizational, procedural and documentation requirements with respect to manufacturing and quality assurance activities. NDA holders using contract manufacturers, laboratories or packagers are responsible for the selection and monitoring of qualified firms, and, in certain circumstances, qualified suppliers to these firms. These firms and, where applicable, their suppliers are subject to inspections by the FDA at any time, and the discovery of violative conditions, including failure to conform to cGMP, could result in enforcement actions that interrupt the operation of any such facilities or the ability to distribute products manufactured, processed or tested by them. Discovery of problems with a product after approval may result in restrictions on a product, manufacturer, or holder of an approved NDA, including, among other things, voluntary recall or withdrawal of the product from the market.

The FDA also may require post-approval testing, sometimes referred to as Phase 4 testing, risk minimization action plans and post-marketing surveillance to monitor the effects of an approved product or place conditions on an approval that could restrict the distribution or use of the product. Discovery of previously unknown problems with a product or the failure to comply with applicable FDA requirements can have negative consequences, including adverse publicity, judicial or administrative enforcement, untitled or warning letters from the FDA, mandated corrective advertising or communications with doctors, and civil or criminal penalties, among others. Newly discovered or developed safety or effectiveness data may require changes to a product's approved labeling, including the addition of new warnings and contraindications, and also may require the implementation of other risk management measures. Also, new government requirements, including those resulting from new legislation, may be established, or the FDA's policies may change, which could delay or prevent regulatory approval of our products under development.

Other Regulatory Matters

Manufacturing, sales, promotion and other activities following product approval are also subject to regulation by numerous regulatory authorities in addition to the FDA, including, in the United States, the Centers for Medicare & Medicaid Services, other divisions of the Department of Health and Human Services, the Drug Enforcement Administration, the Consumer Product Safety Commission, the Federal Trade Commission, the Occupational Safety & Health Administration, the Environmental Protection Agency and state and local governments. In the United States, sales, marketing and scientific/educational programs must also comply with state and federal fraud and abuse laws. Pricing and rebate programs must comply with the Medicaid rebate requirements of the U.S. Omnibus Budget Reconciliation Act of 1990 and more recent requirements in the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010, or ACA. If products are made available to authorized users of the Federal Supply Schedule of the General Services Administration, additional laws and requirements apply. The handling of any controlled substances must comply with the U.S. Controlled Substances Act and Controlled Substances Import and Export Act. Products must meet applicable child-resistant packaging requirements under the U.S. Poison Prevention Packaging Act. Manufacturing, sales, promotion and other activities are also potentially subject to federal and state consumer protection and unfair competition laws.

The distribution of pharmaceutical products is subject to additional requirements and regulations, including extensive record-keeping, licensing, storage and security requirements intended to prevent the unauthorized sale of pharmaceutical products.

The failure to comply with regulatory requirements subjects firms to possible legal or regulatory action. Depending on the circumstances, failure to meet applicable regulatory requirements can result in criminal prosecution, fines or other penalties, injunctions, voluntary recall or seizure of products, total or partial suspension of production, denial or withdrawal of product approvals, or refusal to allow a firm to enter into supply contracts, including government contracts. In addition, even if a firm complies with FDA and other requirements, new information regarding the safety or efficacy of a product could lead the FDA to modify or withdraw product approval. Prohibitions or restrictions on sales or withdrawal of future products marketed by us could materially affect our business in an adverse way.

Changes in regulations, statutes or the interpretation of existing regulations could impact our business in the future by requiring, for example: (i) changes to our manufacturing arrangements; (ii) additions or modifications to product labeling; (iii) the voluntary recall or discontinuation of our products; or (iv) additional record-keeping requirements. If any such changes were to be imposed, they could adversely affect the operation of our business.

U.S. Patent Term Restoration and Marketing Exclusivity

Depending upon the timing, duration and specifics of the FDA approval of our drug candidates, some of our U.S. patents may be eligible for limited patent term extension under the Drug Price Competition and Patent Term Restoration Act of 1984, commonly referred to as the Hatch-Waxman Amendments. The Hatch-Waxman Amendments permit a patent restoration term of up to five years as compensation for patent term lost during product development and the FDA regulatory review process. However, patent term restoration cannot extend the remaining term of a patent beyond a total of 14 years from the product's approval date. The patent term restoration period is generally one-half the time between the effective date of an IND and the submission date of an NDA plus the time between the submission date of an NDA and the approval of that application, minus any time the applicant did not act with due diligence. Only one patent applicable to an approved drug is eligible for the extension and the application for the extension must be submitted prior to the expiration of the patent. The U.S. PTO, in consultation with the FDA, reviews and approves the application for any patent term extension or restoration. In the future, we intend to apply for restoration of patent term for one of our currently owned or licensed patents to add patent life beyond its current expiration date, depending on the expected length of the clinical trials and other factors involved in the filing of the relevant NDA.

Marketing exclusivity provisions under the FDCA can also delay the submission or the approval of certain marketing applications. The FDCA provides a five-year period of non-patent marketing exclusivity within the United States to the first applicant to obtain approval of an NDA for a new chemical entity. A drug is a new chemical entity if the FDA has not previously approved any other new drug containing the same active moiety, which is the molecule or ion responsible for the action of the drug substance. During the exclusivity period, the FDA may not accept for review an abbreviated new drug application, or ANDA, or a 505(b)(2) NDA submitted by another company for another drug based on the same active moiety, regardless of whether the drug is intended for the same indication as the original innovator drug or for another indication, where the applicant does not own or have a legal right of reference to all the data required for approval. However, an application may be submitted after four years if it contains a certification of patent invalidity or non-infringement to one of the patents listed with the FDA by the innovator NDA holder. The FDCA also provides three years of marketing exclusivity for an NDA, or supplement to an existing NDA if new clinical investigations, other than bioavailability studies, that were conducted or sponsored by the applicant are deemed by the FDA to be essential to the approval of the application, for example for new indications, dosages or strengths of an existing drug. This three-year exclusivity covers only the modification for which the drug received approval on the basis of the new clinical investigations and does not prohibit the FDA from approving ANDAs for drugs containing the active agent for the original indication or condition of use. Five-year and three-year exclusivity will not delay the submission or approval of a full NDA. However, an applicant submitting a full NDA would be required to conduct or obtain a right of reference to all of the nonclinical studies and adequate and well-controlled clinical trials necessary to demonstrate safety and effectiveness. Orphan drug exclusivity, as described above, may offer a seven-year period of marketing exclusivity, except in certain circumstances. Pediatric exclusivity is another type of regulatory market exclusivity in the United States. Pediatric exclusivity, if granted, adds six months to existing exclusivity periods and patent terms. This six-month exclusivity, which runs from the end of other exclusivity protection or patent term, may be granted based on the voluntary completion of pediatric trials in accordance with an FDA-issued "Written Request" for such clinical trials.

European Union Drug Development

In the EU our future products may also be subject to extensive regulatory requirements. As in the United States, medicinal products can only be marketed if a marketing authorization from the competent regulatory agencies has been obtained.

Similar to the United States, the various phases of nonclinical and clinical research in the EU are subject to significant regulatory controls. Although the EU Clinical Trials Directive 2001/20/EC has sought to harmonize the EU clinical trials regulatory framework, setting out common rules for the control and authorization of clinical trials in the EU, the EU Member States have transposed and applied the provisions of the Directive differently. This has led to significant variations in the member state regimes. Under the current regime, before a clinical trial can be initiated it must be approved in each of the EU countries where the clinical trial is to be conducted by two distinct bodies: the National Competent Authority, or NCA, and one or more Ethics Committees, or ECs. Under the current regime all suspected unexpected serious adverse reactions to the investigated drug that occur during the clinical trial have to be reported to the NCA and ECs of the Member State where they occurred. In April 2014, the EU adopted a new Clinical Trials Regulation (EU) No 536/2014, which is set to replace the current Clinical Trials Directive 2001/20/EC. It is expected that the new Clinical Trials Regulation will apply in 2019. It will overhaul the current system of approvals for clinical trials in the EU. Specifically, the new legislation, which will be directly applicable in all member states, aims at simplifying and streamlining the approval of clinical trials in the EU. For instance, the new Clinical Trials Regulation provides for a streamlined application procedure via a single entry point and strictly defined deadlines for the assessment of clinical trial applications.

European Union Drug Review and Approval

In the European Economic Area, or EEA, which is comprised of the 28 Member States of the EU plus Norway, Iceland and Liechtenstein, medicinal products can only be commercialized after obtaining a Marketing Authorization, or MA. There are two types of marketing authorizations:

The Community MA, which is issued by the European Commission through the Centralized Procedure, based on the opinion of the Committee for Medicinal Products for Human Use, or CHMP, of the European Medicines Agency, or EMA, and which is valid throughout the entire territory of the EEA. The Centralized Procedure is mandatory for certain types of products, such as biotechnology medicinal products, orphan medicinal products, and medicinal products containing a new active substance indicated for the treatment of AIDS, cancer, neurodegenerative disorders, diabetes, auto-immune and viral diseases. The Centralized Procedure is optional for products containing a new active substance not yet authorized in the EEA, or for products that constitute a significant therapeutic, scientific or technical innovation or which are in the interest of public health in the EU.

National MAs, which are issued by the competent authorities of the Member States of the EEA and only cover their respective territory, are available for products not falling within the mandatory scope of the Centralized Procedure. Where a product has already been authorized for marketing in a Member State of the EEA, this National MA can be recognized in other Member States through the Mutual Recognition Procedure. If the product has not received a National MA in any Member State at the time of application, it can be approved simultaneously in various Member States through the Decentralized Procedure. Under the Decentralized Procedure an identical dossier is submitted to the competent authorities of each of the Member States in which the MA is sought, one of which is selected by the applicant as the Reference Member State, or RMS. The competent authority of the RMS prepares a draft assessment report, a draft summary of the product characteristics, or SmPC, and a draft of the labeling and package leaflet, which are sent to the other Member States (referred to as the Member States Concerned) for their approval. If the Member States Concerned raise no objections, based on a potential serious risk to public health, to the assessment, SmPC, labeling, or packaging proposed by the RMS, the product is subsequently granted a national MA in all the Member States (i.e. in the RMS and the Member States Concerned).

Under the above described procedures, before granting the MA, the EMA or the competent authorities of the Member States of the EEA make an assessment of the risk-benefit balance of the product on the basis of scientific criteria concerning its quality, safety and efficacy.

European Union New Chemical Entity Exclusivity

In the EU, new chemical entities, sometimes referred to as new active substances, qualify for eight years of data exclusivity upon marketing authorization and an additional two years of market exclusivity. This data exclusivity, if granted, prevents regulatory authorities in the EU from referencing the innovator's data to assess a generic application for eight years, after which generic marketing authorization can be submitted, and the innovator's data may be referenced, but not approved for two years. The overall ten-year period will be extended to a maximum of 11 years if, during the first eight years of those ten years, the marketing authorization holder obtains an authorization for one or more new therapeutic indications which,

during the scientific evaluation prior to their authorization, are held to bring a significant clinical benefit in comparison with existing therapies.

European Union Orphan Designation and Exclusivity

In the EU, the European Commission, upon the recommendation of the EMA's Committee for Orphan Medicinal Products grants orphan drug designation to promote the development of products that are intended for the diagnosis, prevention or treatment of life-threatening or chronically debilitating conditions affecting not more than 5 in 10,000 persons in the EU and for which no satisfactory method of diagnosis, prevention, or treatment has been authorized (or the product would be a significant benefit to those affected). Additionally, designation is granted for products intended for the diagnosis, prevention, or treatment of a life-threatening, seriously debilitating or serious and chronic condition and when, without incentives, it is unlikely that sales of the drug in the EU would be sufficient to justify the necessary investment in developing the medicinal product.

In the EU, orphan drug designation entitles a party to financial incentives such as reduction of fees or fee waivers and ten years of market exclusivity is granted following medicinal product approval. This period may be reduced to six years if the orphan drug designation criteria are no longer met, including where it is shown that the product is sufficiently profitable not to justify maintenance of market exclusivity. Orphan drug designation must be requested before submitting an application for marketing approval. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process.

Reimbursement

Sales of our products will depend, in part, on the extent to which our products will be covered by third-party payors, such as government health programs, commercial insurance and managed healthcare organizations. These third-party payors are increasingly reducing reimbursements for medical products and services.

Additionally, the containment of healthcare costs has become a priority of federal and state governments, and the prices of drugs have been a focus in this effort. The U.S. government, state legislatures and foreign governments have shown significant interest in implementing cost-containment programs, including price controls, restrictions on reimbursement and requirements for substitution of generic products. Adoption of price controls and cost-containment measures, and adoption of more restrictive policies in jurisdictions with existing controls and measures, could further limit our net revenue and results. Decreases in third-party reimbursement for our product candidate or a decision by a third-party payor to not cover our product candidate could reduce physician usage of the product candidate and have a material adverse effect on our sales, results of operations and financial condition.

The Medicare Prescription Drug, Improvement, and Modernization Act of 2003, or the MMA, established the Medicare Part D program to provide a voluntary prescription drug benefit to Medicare beneficiaries. Under Part D, Medicare beneficiaries may enroll in prescription drug plans offered by private entities which provide coverage of outpatient prescription drugs. Unlike Medicare Part A and B, Part D coverage is not standardized. Part D prescription drug plan sponsors are not required to pay for all covered Part D drugs, and each drug plan can develop its own drug formulary that identifies which drugs it will cover and at what tier or level. However, Part D prescription drug formularies must include drugs within each therapeutic category and class of covered Part D drugs, though not necessarily all the drugs in each category or class. Any formulary used by a Part D prescription drug plan must be developed and reviewed by a pharmacy and therapeutic committee. Government payment for some of the costs of prescription drugs may increase demand for products for which we receive marketing approval. However, any negotiated prices for our products covered by a Part D prescription drug plan will likely be lower than the prices we might otherwise obtain. Moreover, while the MMA applies only to drug benefits for Medicare beneficiaries, private payors often follow Medicare coverage policy and payment limitations in setting their own payment rates. Any reduction in payment that results from the MMA may result in a similar reduction in payments from non-governmental payors.

The American Recovery and Reinvestment Act of 2009 provides funding for the federal government to compare the effectiveness of different treatments for the same illness. The plan for the research was published in 2012 by the Department of Health and Human Services, the Agency for Healthcare Research and Quality and the National Institutes for Health, and periodic reports on the status of the research and related expenditures are made to Congress. Although the results of the comparative effectiveness studies are not intended to mandate coverage policies for public or private payors, it is not clear what effect, if any, the research will have on the sales of our product candidates, if any such product or the condition that it is intended to treat is the subject of a trial. It is also possible that comparative effectiveness research demonstrating benefits in a competitor's product could adversely affect the sales of our product candidates. If third-party payors do not consider our

products to be cost-effective compared to other available therapies, they may not cover our products after approval as a benefit under their plans or, if they do, the level of payment may not be sufficient to allow us to sell our products on a profitable basis.

The ACA, enacted in March 2010, has a significant impact on the health care industry. The ACA is intended to expand coverage for the uninsured while at the same time containing overall healthcare costs. With regard to pharmaceutical products, among other things, the ACA expands and increases industry rebates for drugs covered under Medicaid programs and makes changes to the coverage requirements under the Medicare Part D program. Pharmaceutical manufacturers are required to track certain financial arrangements with physicians and teaching hospitals, including any "transfer of value" made or distributed to such entities, as well as any investment interests held by physicians and their immediate family members. Manufacturers are required to annually report this information to The Center for Medicare and Medicaid services, or CMS, which posts the information on its website.

Since its enactment, there have been challenges to numerous aspects of the ACA, including efforts to repeal and replace the ACA, and the ACA has been modified in a number of respects. While Congress has not passed repeal legislation to date, the 2017 Tax Reform Act includes a provision repealing the individual mandate, effective January 1, 2019. Further, on January 20, 2017, President Trump signed an Executive Order directing federal agencies with authorities and responsibilities under the ACA to waive, defer, grant exemptions from, or delay the implementation of any provision of the ACA that would impose a fiscal or regulatory burden on states, individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devises. On October 13, 2017, President Trump signed an Executive Order terminating the cost-sharing subsidies that reimburse the insurers under the ACA. Several state Attorneys General filed suit to stop the administration from terminating the subsidies, but their request for a restraining order was denied by a federal judge in California on October 25, 2017. In addition, CMS has proposed regulations that would give states greater flexibility in setting benchmarks for insurers in the individual and small group marketplaces, which may have the effect of relaxing the essential health benefits required under the ACA for plans sold through these marketplaces. Congress will likely consider other legislation to replace elements of the ACA. We cannot predict how the ACA, its possible repeal or replacement, any further action to modify the ACA, or the political uncertainty surrounding the ACA will affect our business.

In addition, other legislative changes have been proposed and adopted in the United States since the ACA was enacted. On August 2, 2011, the Budget Control Act of 2011 among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation's automatic reduction to several government programs. This includes aggregate reductions to Medicare payments to providers of up to 2% per fiscal year, started in April 2013. On January 2, 2013, then President Obama signed into law the American Taxpayer Relief Act of 2012, or the ATRA, which delayed for another two months the budget cuts mandated by these sequestration provisions of the Budget Control Act of 2011. The ATRA, among other things, also reduced Medicare payments to several providers, including hospitals, imaging centers and cancer treatment centers, and increased the statute of limitations period for the government to recover overpayments to providers from three to five years. We expect that additional federal healthcare reform measures will be adopted in the future, any of which could limit the amounts that federal and state governments will pay for healthcare products and services, and in turn could significantly reduce the projected value of certain development projects and reduce our profitability.

In addition, in some foreign countries, the proposed pricing for a drug must be approved before it may be lawfully marketed. The requirements governing drug pricing vary widely from country to country. For example, the EU provides options for its member states to restrict the range of medicinal products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. A member state may approve a specific price for the medicinal product or it may instead adopt a system of direct or indirect controls on the profitability of the company placing the medicinal product on the market. There can be no assurance that any country that has price controls or reimbursement limitations for pharmaceutical products will allow favorable reimbursement and pricing arrangements for any of our products. Historically, products launched in the EU do not follow price structures of the United States and generally tend to be significantly lower.

Other Healthcare Laws and Compliance Requirements

If we obtain regulatory approval of our products, we may be subject to various federal and state laws targeting fraud and abuse in the healthcare industry. These laws may impact, among other things, our proposed sales, marketing and education programs. In addition, we may be subject to patient privacy regulation by both the federal government and the states in which we conduct our business. The laws that may affect our ability to operate include:

- the federal Anti-Kickback Statute, which prohibits, among other things, persons from knowingly and willfully soliciting, receiving, offering or paying remuneration, directly or indirectly, in cash or in kind, to induce or reward, or in return for, either the referral of an individual for, or the purchase, order, or recommendation of, an item or service reimbursable under a federal healthcare program, such as the Medicare and Medicaid programs;
- federal civil and criminal false claims laws and civil monetary penalty laws, which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, claims for payment from Medicare, Medicaid, or other third-party payors that are false or fraudulent, or making a false statement or record material to payment of a false claim or avoiding, decreasing, or concealing an obligation to pay money to the federal government;
- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which created new federal criminal statutes that prohibit executing a scheme to defraud any healthcare benefit program and making false statements relating to healthcare matters;
- the federal transparency laws, including the federal Physician Payment Sunshine Act, which is part of the ACA, that requires applicable manufacturers of covered drugs and biologics to disclose payments and other transfers of value provided to physicians and teaching hospitals and physician ownership and investment interests;
- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act and its implementing regulations, which imposes certain requirements relating to the privacy, security and transmission of individually identifiable health information; and
- state law equivalents of each of the above federal laws, such as anti-kickback and false claims laws which may apply to items or services reimbursed by any third-party payor, including commercial insurers, and state laws governing the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and may not have the same effect, thus complicating compliance efforts.

Employees

As of March 1, 2019, we employed 38 full-time employees, including 29 in research and development and 9 in general and administrative. We have never had a work stoppage, and none of our employees is represented by a labor organization or is under any collective-bargaining arrangements. We consider our employee relations to be good.

Our Corporate Information

We were incorporated under the laws of the State of Delaware in 2005. Our principal executive offices are located at 175 Portland Street, 4th Floor, Boston, MA 02114, and our telephone number is (617) 622-4003. Our website address is www.zafgen.com. We may post material information on our website, therefore please check our website to see if we have posted any material information.

Available Information

We make available free of charge through our website 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 Sections 13(a) and 15(d) of the Securities Exchange Act of 1934, as amended, or the Exchange Act. Please call the Securities and Exchange Commission, or the SEC, at 1-800-SEC-0330 for more information about the operation of the SEC's public reference room. You can review our electronically filed reports and other information that we file with the SEC on the SEC's Internet website at http://www.sec.gov. We also make available, free of charge on our website, the reports filed with the SEC by our executive officers, directors and 10% stockholders pursuant to Section 16 under the Exchange Act as soon as reasonably practicable after copies of those filings are provided to us by those persons. The information contained on, or that can be accessed through, our website is not a part of or incorporated by reference in this Annual Report.

ITEM 1A. RISK FACTORS

Investing in our common stock involves a high degree of risk. You should carefully consider the risks described below, as well as the other information in this Annual Report on Form 10-K, or Annual Report, and in our other public filings before making an investment decision. Our business, prospects, financial condition, or operating results could be harmed by any of these risks, as well as other risks not currently known to us or that we currently consider immaterial. If any such risks or uncertainties actually occur, our business, financial condition or operating results could differ materially from the plans, projections and other forward-looking statements included in the section titled "Management's Discussion and Analysis of Financial Condition and Results of Operations" and elsewhere in this Annual Report and in our other public filings. The trading price of our common stock could decline due to any of these risks, and as a result, you may lose all or part of your investment.

Risks Related to Product Development, Regulatory Approval and Commercialization

We currently depend primarily on the success of one product candidate, ZGN-1061, which has completed a Phase 1 and a Phase 2 clinical trial, but has been placed on a full clinical hold by the FDA. We cannot be certain that we will be able to obtain regulatory approval for ZGN-1061, or successfully commercialize ZGN-1061 if approved.

We currently have only one product candidate in clinical development, ZGN-1061, which has completed a Phase 1 clinical trial in the Netherlands and a Phase 2 clinical trial in Australia and New Zealand, and our business currently depends primarily on its successful clinical development, regulatory approval and commercialization. We currently have no drug products for sale and may never be able to develop marketable drug products. In order to conduct clinical trials in the United States we need approval for our Investigational New Drug, or IND, application with the U.S. Food and Drug Administration, or FDA. Because our business is primarily dependent upon this one product candidate, any setback in our pursuit of regulatory approval for ZGN-1061 would have a material adverse effect on our business and prospects. The clinical trials of our product candidates are, and the manufacturing and marketing of our product candidates will be, subject to extensive and rigorous review and regulation by numerous government authorities in the United States and in other countries where we intend to test and, if approved, market any product candidate. Before obtaining regulatory approvals for the commercial sale of any product candidate, we must demonstrate through nonclinical testing and clinical trials that the product candidate is safe and effective for use in each target indication. This process can take many years and will likely include post-marketing studies, or PMS, post-marketing requirements, or PMRs, and surveillance such as Risk Evaluation and Mitigation Strategies, or REMS, which will require the expenditure of substantial resources beyond the proceeds we currently have on hand.

Furthermore, we are not permitted to market ZGN-1061 in the United States until we receive approval of a New Drug Application, or NDA, from the FDA, or in any foreign countries until we receive the requisite marketing approval from such countries. Development of diabetes drugs requires at least 2,500 subjects randomized to active doses of the product with 1,300 to 1,500 subjects exposed for a year and 300 to 500 subjects exposed for 18 months in order to estimate the safety of the drug in an NDA. In addition, it is anticipated that the FDA may require that their guidance for assessment of cardiovascular, or CV, risk with diabetes products be followed which may require testing of 5,000 to 10,000 subjects. Meeting the requirements of the FDA or certain European regulatory authorities may require that we conduct additional pivotal clinical trials. Accordingly, obtaining approval of an NDA or Marketing Authorization Application, or MAA, is a complex, lengthy, expensive and uncertain process.

The FDA and certain European regulatory authorities may delay, limit or deny approval of ZGN-1061 for many reasons, including, among others:

- the FDA has placed a full clinical hold on the IND for the first U.S. clinical trial of ZGN-1061, citing the possibility of CV safety risk based on our prior compound. Although we are assessing potential paths toward resolution, the full clinical hold raises a number of risks, including but not limited to: we may be required to complete other unexpected work in order to resolve the hold and begin clinical trials in the United States, which can result in development delays; the hold may negatively affect our ability to pursue clinical trials outside of the United States; the hold may make it more difficult to raise capital or to find a commercial partner to execute future clinical trials; or, we may not be able to resolve the full clinical hold at all. Even if we are able to resolve the clinical hold, the FDA may place the IND application on partial hold for ZGN-1061 which could limit the type, condition, and future conduct of clinical trials for ZGN-1061;
- we may not be able to demonstrate that ZGN-1061 is safe and effective to the satisfaction of the FDA and the European Medicines Agency, or EMA;
- the results of our clinical trials may not meet the level of statistical or clinical significance required by the FDA and EMA for marketing approval;

- the FDA and EMA may disagree with the number, design, size, duration, conduct or implementation of our clinical trials;
- the FDA and EMA may require that we conduct additional clinical trials or nonclinical studies;
- the FDA and EMA may not approve the formulation, labeling or specifications of ZGN-1061;
- the contract research organizations, or CROs, that we retain to conduct our clinical trials may take actions outside of our control that materially adversely impact our clinical trials;
- the FDA and EMA may find the data from nonclinical studies and clinical trials insufficient to demonstrate that ZGN-1061's clinical and other benefits outweigh its safety risks;
- the FDA and EMA may disagree with our interpretation of data from our nonclinical studies and clinical trials;
- the FDA and EMA may not accept data generated at our clinical trial sites;
- if and when our NDA is submitted and is determined to require an FDA advisory committee assessment, or the advisory committee may recommend against approval of our application or may recommend that the FDA require, as a condition of approval, additional nonclinical studies or clinical trials, limitations on approved labeling or distribution and use restrictions;
- the FDA could require development of a REMS as a condition of approval or post-approval, or may not agree with our proposed REMS, or may impose additional requirements that limit the promotion, advertising, distribution, or sales of ZGN-1061;
- the FDA and EMA may find deficiencies with or not approve the manufacturing processes or facilities of third-party manufacturers with which we contract; or
- the FDA and EMA may change their approval policies or adopt new regulations.

Any of these factors, many of which are beyond our control, could jeopardize our ability to obtain and/or maintain regulatory approval for and successfully market ZGN-1061. Of the large number of drugs in development in the United States, only a small percentage will successfully complete the FDA regulatory approval process and be commercialized. Accordingly, even if we are able to obtain the requisite financing to continue to fund our development and clinical trials, we cannot assure you that ZGN-1061, ZGN-1258 or any other of our product candidates will be successfully developed or commercialized.

We cannot be certain that we will be able to successfully complete clinical trials for our product candidates, obtain regulatory approval for our product candidates or successfully commercialize our product candidates, if approved.

We currently have only one product candidate in clinical development, ZGN-1061, which has completed a Phase 1 clinical trial in the Netherlands and a Phase 2 clinical trial in Australia and New Zealand, and our business currently depends primarily on its successful clinical development, regulatory approval and commercialization. At the beginning of 2018 we announced a new product candidate, ZGN-1258, which is in nonclinical development. We expect to initially develop ZGN-1258 as a treatment for Prader-Willi syndrome, or PWS. In March 2019, we announced our decision to suspend plans to file an IND for ZGN-1258 in order to evaluate ZGN-1258 following an unexpected finding in muscle tissue in rodent toxicology studies. In the fourth quarter of 2018, we announced a new product candidate, ZGN-1345, which is in nonclinical development. Before our product candidates can be marketed, our IND application or other comparable regulatory approvals must go into effect permitting the conduct of clinical trials, and we must then successfully complete human testing. The FDA and other comparable foreign regulatory agencies must approve our NDA or comparable regulatory submissions. Even after successful completion of clinical testing, there is a risk that the FDA or other regulatory agencies may request further information from us, disagree with our findings or otherwise undertake a lengthy review of our submission. Even if the FDA approves our NDA, we may be unable to successfully commercialize our product candidates.

It is possible that the FDA or other regulatory agencies will not approve any application that we may submit. It is possible that our product candidates may not obtain appropriate regulatory approvals necessary for us to commence clinical trials for our product candidates. Any delay or failure in obtaining required approvals could have a material adverse effect on our business. This process can take many years and will likely require the expenditure of substantial resources beyond the proceeds we currently have on hand.

Favorable results from nonclinical studies and clinical trials to date are not necessarily predictive of the results of additional nonclinical studies or later-stage clinical trials of ZGN-1061. Given the thrombosis findings in humans treated with beloranib, development costs for ZGN-1061 may be higher and we may be unable to successfully develop, obtain regulatory approval for and commercialize ZGN-1061.

Favorable results from our nonclinical studies of ZGN-1061, our Phase 1 clinical trial and analysis of our Phase 2 clinical trial of ZGN-1061 to date, may not necessarily be predictive of the results from ongoing and later-stage clinical trials. Toxicology studies in multiple species have shown that ZGN-1061 is not exhibiting any testicular safety signals or activation of thrombosis-related biochemical markers, and displays an appreciable margin for embryofetal toxicity, testicular toxicity, pro-thrombotic effects and other previously observed issues for MetAP2 inhibitors such as hematological and neuronal toxicities with a small therapeutic margin and no margin for embryofetal toxicity. Further, we have demonstrated in clinical trials that ZGN-1061 demonstrated rapid drug absorption and clearance in line with criteria established in advance for the molecule and has a favorable tolerability profile with no safety signals identified, including no evidence of pro-thrombotic effects. Data from the analysis of the Phase 2 clinical trial to date of ZGN-1061 demonstrated a favorable glycated hemoglobin A1C, or A1C, effect at the two highest doses tested (0.9 mg and 1.8 mg) and accompanying weight loss at the highest dose. However, we can provide no assurance that the results of our nonclinical and clinical studies to date of ZGN-1061 will be replicated in ongoing or later-stage clinical trials of ZGN-1061 or other nonclinical studies.

Many companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in clinical trials after achieving positive results in nonclinical and early-stage clinical development. In particular, we have suffered significant setbacks in later-stage clinical trials of our former lead product candidate, beloranib, after achieving positive results in nonclinical and clinical development, and we cannot be certain that we will not face similar setbacks in our development of ZGN-1061, or our other programs. The setbacks in later-stage clinical development have been caused by, among other things, nonclinical findings made while clinical trials were underway or safety or efficacy observations made in clinical trials, including previously unreported or understood adverse events. Moreover, nonclinical and clinical data are often susceptible to varying interpretations and analyses, and many companies that believed their product candidates performed satisfactorily in nonclinical studies and clinical trials nonetheless failed to obtain FDA and/or EMA approval. If we fail to produce positive results in our later-stage clinical trials of ZGN-1061, the development timeline and regulatory approval and commercialization prospects for our lead product candidate, and, correspondingly, our business and financial prospects, would be materially adversely affected.

Our product candidates may cause undesirable side effects that could delay or prevent their regulatory approval, limit the commercial profile of an approved label, or result in significant negative consequences following marketing approval, if any.

Undesirable side effects caused by our product candidates could cause us or regulatory authorities such as the FDA 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 regulatory authorities. For example, common adverse events observed in patients treated with our first-generation MetAP2 inhibitor, beloranib, versus placebo included diarrhea, injection site bruising, dizziness, decreased appetite, anxiety and sleep disturbances (insomnia principally manifested as delayed onset of sleep and abnormal dreams), among others. In addition, an imbalance in the number of thrombotic events observed in patients treated with beloranib as compared to patients on placebo in our clinical trials was observed. We may see similar adverse events with ZGN-1061 or our other product candidates as we saw with beloranib, and therefore, we are studying these parameters in nonclinical and clinical development of ZGN-1061 and ZGN-1345 and our further evaluation of ZGN-1258. Data from the Phase 2 clinical trial of ZGN-1061 indicated that ZGN-1061 was generally safe and well-tolerated, with primarily mild to moderate adverse events, or AEs. The most frequent treatment emergent AEs with ZGN 1061 in ZAF-1061-201 were injection site bruising, upper respiratory tract infection, and diarrhea; each of these categories of events occurred with relatively similar incidences to placebo. There were no treatment-related serious adverse events and no CV safety signals were observed. In addition, data from the Phase 2 clinical trial of ZGN-1061 demonstrated a beneficial decrease in A1C in the 0.9 mg and 1.8 mg dose groups and accompanying weight loss in the 1.8 mg dose group through the 12-week assessment period, and it is unknown whether this effect would continue beyond 12 weeks.

Further, if ZGN-1061, ZGN-1258 (if further evaluation warrants continued development) and ZGN-1345 receive marketing approval and we or others identify undesirable side effects caused by the product (or any other similar product) after the approval, a number of potentially significant negative consequences could result, including:

- regulatory authorities may request that we withdraw the product from the market or may limit their approval of the product through labeling or other means;

- regulatory authorities may require the addition of labeling statements, such as a "black box" warning or a contraindication or a precaution;
- we may be required to change the way the product is distributed or administered, conduct additional clinical trials or change the labeling of the product;
- we may decide to remove the product from the marketplace;
- we could be sued and held liable for injury caused to individuals exposed to or taking our product candidates; and
- our reputation may suffer.

Any of these events could prevent us from achieving or maintaining market acceptance of the affected product candidate and could substantially increase the costs of commercializing our product candidates and significantly impact our ability to successfully commercialize our product candidates and generate revenues.

Failures or delays in the commencement or completion of our planned clinical trials of ZGN-1061, ZGN-1258 and ZGN-1345 could result in increased costs to us and could delay, prevent or limit our ability to generate revenue and continue our business.

ZGN-1061 has completed a Phase 1 clinical trial in the Netherlands and a Phase 2 clinical trial conducted in Australia and New Zealand and will require substantial further clinical development before we can submit an NDA to the FDA or an MAA to the EMA for its marketing approval. ZGN-1258 and ZGN-1345 are still in nonclinical development, and additional nonclinical work must be completed prior to filing the IND application with the FDA and to commence into clinical trials. In March 2019, we announced our decision to suspend plans to file an IND for ZGN-1258 in order to evaluate ZGN-1258 following an unexpected finding in muscle tissue in rodent toxicology studies.

Despite the guidance we may receive from the FDA, the EMA, or other applicable regulatory authorities including Australia and New Zealand, any of these regulatory authorities can change their positions on the acceptability of our clinical trial designs or the clinical endpoints selected, which may require us to complete additional clinical trials or impose stricter approval conditions than we currently expect. Successful completion of such clinical trials is a prerequisite to submitting an NDA to the FDA and an MAA to the EMA and, consequently, the ultimate approval and commercial marketing of ZGN-1061, ZGN-1258 or ZGN-1345. We do not know whether any clinical trials for ZGN-1061, ZGN-1258 or ZGN-1345 will begin or be completed on schedule, if at all, as the commencement and completion of clinical trials can be delayed or prevented for a number of reasons, including, among others:

- the FDA, EMA or other governing bodies in Europe or Australia and New Zealand may deny permission to begin or continue clinical trials, including for certain indications, we want to conduct;
- delays in regulatory filings or receiving regulatory authorizations of IND applications, or clinical trial authorization applications, or CTAs, that may be required;
- unfavorable results from our nonclinical studies, thus the FDA, the EMA or the applicable regulatory authorities in Australia or New Zealand, may require additional nonclinical studies;
- delays in reaching or failing to reach agreement on acceptable terms with prospective CROs and clinical trial sites, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and trial sites;
- inadequate quantity or quality of a product candidate or other materials necessary to conduct clinical trials, for example delays in the manufacturing of sufficient supply of finished drug product;
- difficulties obtaining Institutional Review Board, or IRB, and/or ethics committee approval to conduct a clinical trial at a prospective site or sites in the United States, the European Union, or EU, Australia or New Zealand;
- challenges in recruiting and enrolling patients to participate in clinical trials, including the size and nature of the patient population, the proximity of patients to clinical trial sites, eligibility criteria for the clinical trial, the nature of the clinical trial protocol, the availability of approved effective treatments for the relevant disease and competition from other clinical trial programs for similar indications;
- difficulties in retaining or recruiting clinical investigators and/or patients in our ongoing or future clinical trials;

- difficulties retaining patients who have enrolled in a clinical trial but may be prone to withdraw due to rigors of the clinical trial, lack of efficacy, side effects, screening and monitoring measures, personal issues or loss of interest;
- severe or unexpected drug-related side effects experienced by patients in a clinical trial, including side effects previously identified in our previous clinical trials for beloranib;
- the FDA, the EMA, or the applicable regulatory authorities in Australia and New Zealand may disagree with our clinical trial designs, our interpretation of data from clinical trials, or may change the requirements for approval even after it has reviewed and commented on the design for our clinical trials; and
- reports from nonclinical or clinical testing of other therapies that raise safety or efficacy concerns.

Clinical trials may also be delayed or terminated as a result of ambiguous or negative interim results. In addition, a clinical trial may be suspended or terminated by us, the FDA, other regulatory authorities, the IRBs or ethics committees, at the sites where the IRBs or ethics committees are overseeing a clinical trial, a data monitoring committee, or DMC, overseeing the clinical trial at issue or other regulatory authorities due to a number of factors, including, among others:

- failure to conduct the clinical trial in accordance with regulatory requirements or our clinical protocols;
- inspection of the clinical trial operations or trial sites by the FDA, the EMA, or the applicable regulatory authorities in Australia and New Zealand that reveals deficiencies or violations that require us to undertake corrective action, including the imposition of a partial clinical hold or a full clinical hold;
- unforeseen safety issues, including any that could be identified in our nonclinical studies, adverse side effects or lack of effectiveness;
- changes in government regulations or administrative actions;
- problems with clinical supply materials; and
- lack of adequate funding to continue the clinical trial.

Changes in regulatory requirements, FDA guidance or guidance from EMA, Australia or New Zealand or unanticipated events during our clinical trials of ZGN-1061 or our other product candidates, may occur, which may result in changes to clinical trial protocols or additional clinical trial requirements, which could result in increased costs to us and could delay our development timeline.

Changes in regulatory requirements, FDA guidance or guidance from EMA or unanticipated events during our clinical trials may force us to adjust our clinical program. The FDA, the EMA, or the applicable regulatory authorities in Australia and New Zealand may impose additional clinical trial and/or nonclinical study requirements. For instance, the FDA issued draft guidance on developing products for weight management in February 2007 and issued draft guidance on developing products for the treatment of diabetes in February 2008 but these guidance documents may be revised at any time. In December 2008, FDA established guidance on evaluating CV risk of new therapies for the treatment of type 2 diabetes. Amendments to our clinical trial protocols would require resubmission to the FDA, the EMA, or the applicable regulatory authorities in Australia and New Zealand as well as IRBs and ethics committees for review and approval, which may adversely impact the cost, timing or successful completion of a clinical trial. If we experience delays completing, or if we terminate, any of our clinical trials, or if we are required to conduct additional clinical trials and/or nonclinical studies, the commercial prospects for ZGN-1061 or our other product candidates may be harmed and our ability to generate product revenue will be delayed.

We rely, and expect that we will continue to rely, on third parties to conduct any future clinical trials for ZGN-1061 or our other product candidates. If these third parties do not successfully carry out their contractual duties or meet expected deadlines, we may not be able to develop and obtain regulatory approval for or commercialize ZGN-1061 or our other product candidates, and our business could be substantially harmed.

We enter into agreements with third-party CROs to provide monitors for and to manage data for our ongoing clinical trials. We rely heavily on these parties for execution of clinical trials for ZGN-1061 and will continue to rely on these parties for clinical trials for our other product candidates, if any, but we only control certain aspects of their activities. As a result, we have less direct control over the conduct, timing and completion of these clinical trials and the management of data developed through the clinical trials than would be the case if we were relying entirely upon our own staff. Communicating

with outside parties can also be challenging, potentially leading to mistakes as well as difficulties in coordinating activities. Outside parties may:

- have staffing difficulties;
- fail to comply with contractual obligations;
- experience regulatory compliance issues;
- undergo changes in priorities or become financially distressed; or
- form relationships with other entities, some of which may be our competitors.

These factors may materially adversely affect the willingness or ability of third parties to conduct our clinical trials and may subject us to unexpected cost increases that are beyond our control. Nevertheless, we are responsible for ensuring that each of our clinical trials is conducted in accordance with the applicable protocol, legal and regulatory requirements and scientific standards, and our reliance on CROs does not relieve us of our regulatory responsibilities. We and our CROs are required to comply with requirements for Good Clinical Practice, or GCPs, which are legal requirements enforced by the FDA, the Competent Authorities of the Member States of the European Economic Area and comparable foreign regulatory authorities for any products in clinical development. The FDA enforces these GCP regulations through periodic inspections of clinical trial sponsors, principal investigators and clinical trial sites, IRBs, and other vendors that may be involved in the clinical development of new products. If we or our investigators or CROs fail to comply with applicable GCPs, the clinical data generated in our clinical trials may be deemed unreliable and the FDA or comparable foreign regulatory authorities may require us to perform additional clinical trials before approving our marketing applications. We cannot assure you that, upon inspection, the FDA will determine that any of our clinical trials comply with GCPs. In addition, our clinical trials must be conducted with products produced under current Good Manufacturing Practices, or cGMPs' regulations, to assure the identity, strength, quality, and purity of our drug product candidates being used in the clinical trials, as well as the to-be-marketed formulation and product. Our failure or the failure of our CROs and/or contract manufacturing organizations, or CMOs, to comply with these regulations may require us to repeat clinical trials, which would delay the regulatory approval process and could also subject us to enforcement action, up to and including, civil and criminal penalties.

Although we design our clinical trials, investigators and CROs conduct all of the clinical trials. As a result, many important aspects of our drug development programs are outside of our direct control. In addition, the investigators or CROs may not perform all of their obligations under arrangements with us or in compliance with regulatory requirements, but we remain responsible and are subject to enforcement action that may include civil penalties up to and including criminal prosecution for any violations of FDA laws and regulations during the conduct of our clinical trials. If the investigators or CROs do not perform clinical trials in a satisfactory manner, breach their obligations to us, or fail to comply with regulatory requirements, the development and commercialization of ZGN-1061 or our other product candidates may be delayed or our development program materially and irreversibly harmed. We cannot control the amount and timing of resources these investigators or CROs devote to our program, ZGN-1061, or will devote to or our other product candidates. If we are unable to rely on clinical data collected by our investigators or CROs, we could be required to repeat, extend the duration of, or increase the size of our clinical trials and this could significantly delay commercialization and require significantly greater expenditures.

If any of our relationships with these third-party investigators or CROs terminate, we may not be able to enter into arrangements with alternative investigators or CROs in a timely manner, or at all. If investigators or CROs do not successfully carry out their contractual duties or obligations or meet expected deadlines, if they need to be replaced or if the quality or accuracy of the clinical data they obtain is compromised due to the failure to adhere to our clinical protocols, regulatory requirements or for other reasons, any such clinical trials may be extended, delayed or terminated, and we may not be able to obtain regulatory approval for or successfully commercialize ZGN-1061 or our other product candidates. As a result, our financial results and the commercial prospects for ZGN-1061 or our other product candidates in the subject indications would be harmed, our costs could increase and our ability to generate revenue could be delayed.

The number of patients suffering from PWS is small and has not been established with precision. If the actual number of patients with this condition is smaller than we estimate or if any approval that we obtain is based on a narrower definition of this patient population, our revenue and ability to achieve profitability for any product candidates targeting PWS will be adversely affected, possibly materially.

There is no current comprehensive patient registry or other method of establishing with precision the actual number of patients with PWS in any geography. Published population studies estimate that the prevalence of PWS in the United States and in the EU, ranges from 1 in 8,000 to 1 in 50,000. If the actual number of patients with PWS is lower than we believe or if

any approval that we obtain is based on a narrower definition of these patient populations, then the potential market for any product candidates targeting PWS for these indications will be smaller than we anticipate. If our IND goes into effect, our inability to enroll a sufficient number of patients for our clinical trials could result in significant delays or may require us to abandon one or more clinical trials altogether. Enrollment delays in our clinical trials may result in increased development costs for any product candidates targeting PWS, delay or halt the development of and approval processes for our product candidates and jeopardize our ability to achieve our clinical development timeline and goals, including the dates by which we will commence, complete and receive results from clinical trials. Enrollment delays in our clinical trials may also jeopardize our ability to commence sales of and generate revenues from our product candidates, which could cause the value of our company to decline and limit our ability to obtain additional financing, if needed.

We rely completely on third-party suppliers to manufacture our clinical drug supplies for ZGN-1061 and our other product candidates, and to the extent we elect to commercialize ZGN-1061 or our other product candidates on our own, we intend to rely on third parties to produce commercial supplies of such products, and nonclinical, clinical and commercial supplies of any future product candidate.

We do not currently have, nor do we currently plan to acquire, the infrastructure or capability to internally manufacture our clinical drug supply of ZGN-1061 or any of our other product candidates, for use in the conduct of our nonclinical studies and clinical trials, and we lack the internal resources and the capability to manufacture any product candidates on a clinical or commercial scale. The CMOs used to manufacture the active drug substance and final drug product must be approved by our quality assurance unit and inspected by the FDA and other comparable foreign regulatory agencies.

We rely on our CMOs to comply with cGMPs for manufacture of starting materials, active drug substance and finished drug products. If our CMOs cannot successfully manufacture material that conforms to our specifications and the regulatory requirements of the FDA or applicable foreign regulatory agencies, the CMOs will not be able to secure and/or maintain regulatory approval for their manufacturing facilities or regulatory agencies may find deficiencies with their facilities and refuse to approve our marketing applications. While we manage our quality expectations through an audit program for our vendors and suppliers, we have no direct control over our CMOs' ability to maintain adequate quality control, quality assurance and qualified personnel. Furthermore, our CMOs are engaged with third party vendors to supply and/or manufacture starting materials or components for them, which exposes our CMOs to regulatory risks for the production of such materials and components. As a result, failure to satisfy the regulatory requirements for the production of those materials and components may affect supply. If the FDA or an applicable foreign regulatory agency finds deficiencies with or does not approve these facilities for the manufacture of our product candidates or if it withdraws its approval in the future, we may need to find alternative manufacturing facilities, which would adversely impact our ability to develop, obtain regulatory approval for or market our product candidates.

We rely completely on third-party suppliers to manufacture our nonclinical and clinical drug supplies for ZGN-1061 and our nonclinical drug supplies and future clinical drug supplies for our other product candidates. Currently each batch of ZGN-1061, ZGN-1258 and ZGN-1345 is individually contracted under a work order, which is governed by a quality and service agreement. There is sufficient supply of ZGN-1258 drug substance to support any clinical trials of ZGN-1258 through Phase 2 should our evaluations warrant further development of ZGN-1258. At later stages of development, the drug substance manufacturing process may be further optimized to support advanced clinical development and commercialization. A new formulation with longer shelf life has been developed and manufactured to support clinical development for ZGN-1061.

Even if we receive marketing approval for a product candidate in the United States, we may never receive regulatory approval to market such product candidate outside of the United States.

We may pursue marketing approval for certain of our product candidates in the United States, the EU and in other countries worldwide. In order to market any product outside of the United States, we must establish and comply with the numerous and varying safety, efficacy and other regulatory requirements of other countries, including potential additional clinical trials and/or nonclinical studies. Approval procedures vary among countries and can involve additional product candidate testing and additional administrative review periods. The time required to obtain approvals in other countries might differ from that required to obtain FDA approval. The marketing approval processes in other countries may implicate all of the risks detailed above regarding FDA approval in the United States as well as other risks. In particular, in many countries outside of the United States, products must receive pricing and reimbursement approval before the product can be commercialized. Obtaining this approval can result in substantial delays in bringing products to market in such countries. In addition, on March 20, 2017, the United Kingdom government started the process to leave the EU by April 2019, or Brexit. The effects of Brexit will depend on any agreements the United Kingdom makes to retain access to EU markets either during a transitional period or more permanently. Brexit could lead to legal uncertainty and potentially divergent national laws and

regulation as the United Kingdom determines which EU laws to replace or replicate. Marketing approval in one country does not necessarily ensure marketing approval in another, but a failure or delay in obtaining marketing approval in one country may have a negative effect on the regulatory process or commercial activities in others. Failure to obtain marketing approval in other countries or any delay or other setback in obtaining such approval would impair our ability to market a product candidate in such foreign markets. Any such impairment would reduce the size of our potential market, which could have a material adverse impact on our business, results of operations and prospects.

Even if we receive marketing approval for a product candidate, it may not achieve broad market acceptance, which would limit the revenue that we generate from its sales.

The commercial success of a product candidate, if developed and approved for marketing by the FDA or EMA or other applicable regulatory authorities, will depend upon the awareness and acceptance of our product candidates among the medical community, including physicians, patients, advocacy groups and healthcare payors. Market acceptance of a product candidate, if approved, will depend on a number of factors, including, among others:

- the relative convenience and ease of subcutaneous injections as the necessary method of administration of most of our product candidates;
- the prevalence and severity of any adverse side effects associated with a product candidate;
- limitations or warnings contained in the labeling approved for a product candidate by the FDA, EMA, or other regulatory authorities, such as a "black box" warning;
- availability of alternative treatments, including a number of competitive type 2 diabetes therapies already approved or expected to be commercially launched in the near future and/or future availability of newly approved treatments currently in development for PWS;
- the willingness of the target patient population to try new therapies and of physicians to prescribe these therapies;
- the strength of marketing and distribution support and timing of market introduction of competitive products;
- publicity concerning our products or competing products and treatments;
- pricing;
- the effectiveness of our sales and marketing strategies;
- our ability to increase awareness of a product candidate through marketing efforts;
- our ability to obtain sufficient third-party coverage or reimbursement;
- the willingness of patients to pay out-of-pocket in the absence of third-party coverage; and
- the likelihood that the FDA may require development of a REMS, as a condition of approval or post-approval or may not agree with our proposed REMS or may impose additional requirements that limit the promotion, advertising, distribution or sales of our product candidates.

If a product candidate is approved but does not achieve an adequate level of acceptance by patients, advocacy groups, physicians and payors, we may not generate sufficient revenue from a product candidate to become or remain profitable. Before granting reimbursement approval, healthcare payors may require us to demonstrate that, in addition to treating type 2 diabetes in patients, a product candidate also provides incremental health benefits to patients. Our efforts to educate the medical community and third-party payors about the benefits of a product candidate may require significant resources and may never be successful.

If we are unable to establish sales and marketing capabilities or enter into agreements with third parties to market and sell a product candidate, we may not be able to generate any revenue.

We do not currently have an established infrastructure for the sales, marketing and distribution of pharmaceutical products. In order to market a product candidate, if approved by the FDA or any other regulatory body, we must build our sales, marketing, managerial and other non-technical capabilities or make arrangements with third parties to perform these services. If we are unable to establish adequate sales, marketing and distribution capabilities, whether independently or with third parties, or if we are unable to do so on commercially reasonable terms, our business, results of operations, financial condition and prospects will be materially adversely affected.

Even if we receive marketing approval for a product candidate, we may still face future development and regulatory difficulties.

Even if we receive marketing approval for a product candidate, regulatory authorities may still impose significant restrictions on our product candidates' indicated uses or marketing or impose ongoing requirements for potentially costly post-approval studies. A product candidate will also be subject to ongoing FDA and EMA requirements governing the labeling, packaging, storage and promotion of the product and recordkeeping and submission of safety and other post-market information. The FDA has significant post-market authority, including, for example, the authority to require labeling changes based on new safety information and to require post-market studies or clinical trials to evaluate serious safety risks related to the use of a drug. The FDA also has the authority to require, as part of an NDA or post-approval, the submission of a REMS. Any REMS required by the FDA may lead to increased costs to assure compliance with new post-approval regulatory requirements and potential requirements or restrictions on the sale of approved products, all of which could lead to lower sales volume and revenue. Additionally, the FDA may require a PMS and/or PMRs, that could represent and result in additional restrictions and/or limitations for the product.

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 cGMPs and other regulations. If we or a regulatory agency discover problems with a product candidate, such as adverse events of unanticipated severity or frequency, or problems with the facility where a product candidate is manufactured, a regulatory agency may impose restrictions on a product candidate, the manufacturer or us, including requiring withdrawal of a product candidate from the market or suspension of manufacturing. If we or the manufacturing facilities for a product candidate fail to comply with applicable regulatory requirements, a regulatory agency may, among other things:

- issue warning letters or untitled letters;
- seek an injunction or impose civil or criminal penalties or monetary fines;
- suspend or withdraw marketing approval;
- suspend any ongoing clinical trials;
- refuse to approve pending applications or supplements to applications submitted 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 request that we initiate a product recall.

Competing technologies could emerge, including devices and surgical procedures, adversely affecting our opportunity to generate revenue from the sale of ZGN-1061 or our other product candidates.

The biotechnology and pharmaceutical industries are intensely competitive and subject to rapid and significant technological change. We have competitors in a number of jurisdictions, many of which have substantially greater name recognition, commercial infrastructures and financial, technical and personnel resources than we have. Established competitors may invest heavily to quickly discover and develop novel compounds that could make ZGN-1061 or our other product candidates obsolete or uneconomical. Any new product that competes with an approved product may need to demonstrate compelling advantages in efficacy, convenience, tolerability and safety to be commercially successful. Other competitive factors, including generic competition, could force us to lower prices or could result in reduced sales. In addition, new products developed by others could emerge as competitors to ZGN-1061 or our other product candidates. If we are not able to compete effectively against our current and future competitors, our business will not grow and our financial condition and operations will suffer.

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

Our future profitability will depend, in part, on our ability to commercialize a product candidate in foreign markets for which we may rely on collaborations with third parties. If we commercialize a product candidate in foreign markets, we would be subject to additional risks and uncertainties, including:

- our customers' ability to obtain reimbursement for a product candidate in foreign markets;
- our inability to directly control commercial activities because we are relying on third parties;

- the burden of complying with complex and changing foreign regulatory, tax, accounting and legal requirements;
- different medical practices and customs in foreign countries affecting acceptance in the marketplace;
- import or export licensing requirements;
- longer accounts receivable collection times;
- longer lead times for shipping;
- language barriers for technical training;
- reduced protection of intellectual property rights in some foreign countries;
- foreign currency exchange rate fluctuations; and
- the interpretation of contractual provisions governed by foreign laws in the event of a contract dispute.

Foreign sales of a product candidate could also be adversely affected by the imposition of governmental controls, political and economic instability, trade restrictions and changes in tariffs.

We are subject to healthcare laws and regulations, and health information privacy and security laws, which could expose us to criminal sanctions, civil penalties, contractual damages, reputational harm and diminished profits and future earnings.

Healthcare providers, physicians and others will play a primary role in the recommendation and prescription of ZGN-1061 or our other product candidates, if approved. Our future arrangements with third-party payors will expose us to broadly applicable fraud and abuse and other healthcare laws and regulations that may constrain the business or financial arrangements and relationships through which we market, sell and distribute ZGN-1061 or our other product candidates, if we obtain marketing approval. In addition, we may be subject to patient privacy regulation by both the federal government and the states in which we conduct our business. Restrictions under applicable federal and state healthcare laws and regulations include the following:

- the federal Anti-Kickback Statute prohibits, among other things, persons from knowingly and willfully soliciting, offering, receiving or paying remuneration, directly or indirectly, in cash or in kind, to induce or reward either the referral of an individual for, or the purchase, order or recommendation of, any good or service, for which payment may be made under federal healthcare programs such as Medicare and Medicaid;
- the federal false claims laws impose criminal and civil penalties, including those from civil whistleblower or qui tam actions pursuant to the federal False Claims Act, against individuals or entities for knowingly presenting, or causing to be presented, to the federal government, claims for payment that are false or fraudulent or making a false statement to avoid, decrease, or conceal an obligation to pay money to the federal government;
- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, imposes criminal and civil liability for executing a scheme to defraud any healthcare benefit program and also imposes obligations, including mandatory contractual terms, with respect to safeguarding the privacy, security and transmission of individually identifiable health information;
- the federal false statements statute prohibits knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false statement in connection with the delivery of or payment for healthcare benefits, items or services;
- the federal transparency requirements, sometimes referred to as the "Sunshine Act," under the Patient Protection and Affordable Care Act, require manufacturers of drugs, devices, biologics, and medical supplies to report to the Department of Health and Human Services information related to physician payments and other transfers of value and physician ownership and investment interests;
- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act of 2009, and their respective implementing regulations, which impose requirements on certain covered healthcare providers, health plans, and healthcare clearinghouses as well as their respective business associates that perform services for them that involve the use, or disclosure of, individually identifiable health information, relating to the privacy, security and transmission of individually identifiable health information;

- federal consumer protection and unfair competition laws, which broadly regulate marketplace activities and activities that potentially harm consumers; and
- analogous state laws and regulations, such as state anti-kickback and false claims laws and transparency laws, may apply to sales or marketing arrangements and claims involving healthcare items or services reimbursed by non-governmental third-party payors, including private insurers, and some state laws require pharmaceutical companies to comply with the pharmaceutical industry's voluntary compliance guidelines and the relevant compliance guidance promulgated by the federal government in addition to requiring drug manufacturers to report information related to payments to physicians and other healthcare providers or marketing expenditures and drug pricing.

Ensuring that our future business arrangements with third parties comply with applicable healthcare laws and regulations could be costly. It is possible that governmental authorities will conclude that our business practices do not comply with current or future statutes, regulations or case law involving applicable fraud and abuse or other healthcare laws and regulations. If our operations, including anticipated activities to be conducted by our sales team, were found to be in violation of any of these laws or any other governmental regulations that may apply to us, we may be subject to significant civil, criminal and administrative penalties, damages, fines and exclusion from government funded healthcare programs, such as Medicare and Medicaid, any of which could substantially disrupt our operations. If any of the physicians or other providers or entities with whom we expect to do business is found not to be in compliance with applicable laws, they may be subject to criminal, civil or administrative sanctions, including exclusions from government funded healthcare programs.

In addition, regulators globally are also imposing greater monetary fines for privacy violations. For example, in 2016, the EU adopted a new regulation governing data practices and privacy called the General Data Protection Regulation, or GDPR, which became effective on May 25, 2018. The GDPR applies to any company established in the EU as well as to those outside the EU if they collect and use personal data in connection with the offering of goods or services to individuals in the EU or the monitoring of their behavior. The GDPR enhances data protection obligations for processors and controllers of personal data, including, for example, expanded disclosures about how personal information is to be used, limitations on retention of information, mandatory data breach notification requirements and onerous new obligations on service providers. Non-compliance with the GDPR may result in monetary penalties of up to €20 million or 4% of worldwide revenue, whichever is higher. The GDPR and other changes in laws or regulations associated with the enhanced protection of certain types of personal data, such as healthcare data or other sensitive information, could greatly increase our cost of providing our products and services or even prevent us from offering certain services in jurisdictions that we operate.

The FDA and other regulatory agencies actively enforce the laws and regulations prohibiting the promotion of off-label uses. If we are found to have improperly promoted off-label uses, we may become subject to significant liability.

The FDA and other regulatory agencies strictly regulate the promotional claims that may be made about prescription products, such as ZGN-1061 or our other product candidates, if approved. If we receive marketing approval for ZGN-1061, or our other product candidates, physicians may prescribe our product candidates to their patients in a manner that is inconsistent with the approved label. If we are found to have promoted such off-label uses, we may become subject to significant liability. The federal government has levied large civil and criminal fines against companies for alleged improper promotion and has enjoined several companies from engaging in off-label promotion and required that they enter into corporate integrity agreements with the Office of Inspector General of the Department of Health and Human Services, or OIG. The FDA has also requested that companies enter into consent decrees or permanent injunctions under which specified promotional conduct is changed or curtailed. If we cannot successfully manage the promotion of ZGN-1061 or our other product candidates, if approved, we could become subject to significant liability, which would materially adversely affect our business and financial condition.

Even if approved, reimbursement policies could limit our ability to sell product candidates that we elect to sell on our own.

If approved by regulatory authorities, market acceptance and sales of product candidates that we elect to sell on our own will depend on reimbursement policies and may be affected by healthcare reform measures. Government authorities and third-party payors, such as private health insurers and health maintenance organizations, decide which medications they will pay for and establish reimbursement levels for those medications. Cost containment is a primary concern in the U.S. healthcare industry and elsewhere. Government authorities and these third-party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular medications. We cannot be sure that reimbursement will be available for product candidates that we elect to sell on our own and, if reimbursement is available, the level of such reimbursement. Reimbursement may impact the demand for, or the price of, product candidates that we elect to sell on our

own. If reimbursement is not available or is available only at limited levels, we may not be able to successfully commercialize product candidates that we elect to sell on our own.

In some foreign countries, particularly in Canada and European countries, the pricing of prescription pharmaceuticals is subject to strict governmental control. In these countries, pricing negotiations with governmental authorities can take six to 12 months or longer after the receipt of regulatory approval and product launch. To obtain favorable reimbursement for the indications sought or pricing approval in some countries, we may be required to conduct a clinical trial that compares the cost-effectiveness of product candidates that we elect to sell on our own with other available therapies. If reimbursement for product candidates that we elect to sell on our own is unavailable in any country in which we seek reimbursement, if it is limited in scope or amount, if it is conditioned upon our completion of additional clinical trials, or if pricing is set at unsatisfactory levels, our operating results could be materially adversely affected.

Recently enacted and future legislation may increase the difficulty and cost for us to obtain regulatory approval of and commercialize our drug candidates and affect the prices we may obtain.

The Affordable Care Act, or the ACA, has a significant impact on the healthcare industry. The ACA is a sweeping law intended to broaden access to health insurance, reduce or constrain the growth of healthcare spending, enhance remedies against fraud and abuse, add new transparency requirements for the healthcare and health insurance industries, impose new taxes and fees on the health industry and impose additional health policy reforms. The current presidential administration has indicated that enacting changes to the ACA is a legislative priority and has alternatively discussed repealing and replacing the ACA. While Congress has not passed repeal legislation to date, the 2017 Tax Reform Act includes a provision repealing the individual mandate, effective January 1, 2019. Further, on January 20, 2017, President Trump signed an Executive Order directing federal agencies with authorities and responsibilities under the ACA to waive, defer, grant exemptions from, or delay the implementation of any provision of the ACA that would impose a fiscal burden on states or a cost, fee, tax, penalty or regulatory burden on individuals, healthcare providers, health insurers, or manufacturers of pharmaceuticals or medical devices. On October 13, 2017, President Trump signed an Executive Order terminating the cost-sharing subsidies that reimburse insurers under the ACA. In addition, the Centers for Medicare and Medicaid Services, or CMS, has proposed regulations that would give states greater flexibility in setting benchmarks for insurers in the individual and small group marketplaces, which may have the effect of relaxing the essential health benefits required under the ACA for plans sold through these marketplaces. Congress will likely consider other legislation to replace elements of the ACA. We do not know at this time what implications these changes and other, proposed changes, if enacted, would have on the ACA's current requirements or on our future business. Changes to the ACA or other existing health care regulations could significantly impact our business and the pharmaceutical industry.

We may seek to obtain orphan drug designation for certain of our product candidates, and we may be unsuccessful.

As part of our business strategy, we may seek to obtain orphan drug designation for certain of our product candidates in the United States and the EU. We may be unsuccessful in obtaining orphan drug designation, and if we do, we may not receive orphan drug exclusivity for these products. In the United States, the company that first obtains FDA approval for a designated orphan drug for the specified rare disease or condition receives orphan drug marketing exclusivity for that drug for a period of seven years. This orphan drug exclusivity prevents the FDA from approving another application, including a full NDA to market the same drug for the same orphan indication, except in very limited circumstances, including when the FDA concludes that the later drug is safer, more effective or makes a major contribution to patient care. For purposes of small molecule drugs, the FDA defines "same drug" as a drug that contains the same active chemical entity and is intended for the same use as the drug in question. A designated orphan drug may not receive orphan drug exclusivity if it is approved for a use that is broader than the indication for which it received orphan designation. Orphan drug exclusive marketing rights in the United States may be lost if the FDA later determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantity of the drug to meet the needs of patients with the rare disease or condition.

Our development programs for our product candidates, which are primarily related to ZGN-1061, ZGN-1258 and ZGN-1345, may require substantial financial resources and may ultimately be unsuccessful.

Our lead product candidate ZGN-1061 has completed a Phase 1 clinical trial and is currently in Phase 2 clinical development, and there are a number of FDA and certain European regulatory requirements that we must satisfy before we can commence late-stage clinical trials of ZGN-1061. Satisfaction of these requirements will entail substantial time, effort and financial resources. We may never satisfy these requirements. ZGN-1258 is currently being evaluated following our March 2019 announcement to suspend plans to file an IND for ZGN-1258 based on an unexpected finding in muscle tissue in rodent toxicology studies and ZGN-1345 is still in nonclinical development. We believe that our cash, cash equivalents and

marketable securities will be sufficient to fund operations for a period of at least one year from the issuance date of this Annual Report, but we will need to raise more funds to continue development and commercialization of ZGN-1061, ZGN-1258 (if further evaluations warrant its continued development and commercialization), ZGN-1345 and our other product candidates, which may not be easily available. Furthermore, any time, effort and financial resources we expend on our other early-stage development programs may adversely affect our ability to continue development and commercialization of ZGN-1061, ZGN-1258 (if further evaluations warrant its continued development and commercialization) and ZGN-1345, and we may never commence clinical trials of such development programs despite expending significant resources in pursuit of their development. If we do commence clinical trials of our other potential product candidates, such product candidates may never be approved by the FDA or other regulatory authorities.

Risks Related to Our Intellectual Property Rights

If we are unable to adequately protect our proprietary technology or maintain issued patents which are sufficient to protect ZGN-1061, ZGN-1258, ZGN-1345 or future product candidates, others could compete against us more directly, which would have a material adverse impact on our business, results of operations, financial condition and prospects.

Our commercial success will depend in part on our success in obtaining and maintaining issued patents and other intellectual property rights in the United States and elsewhere and protecting our proprietary technology. If we do not adequately protect our intellectual property and proprietary technology, competitors may be able to use our technologies and erode or negate any competitive advantage we may have, which could harm our business and ability to achieve profitability.

As of March 1, 2019, we own two issued U.S. patents, two pending U.S. patent applications and related pending foreign counterpart patent applications, as well as one pending Patent Cooperation Treaty, or PCT patent application, and three pending U.S. provisional patent applications that relate to ZGN-1061.

As of March 1, 2019, we own one issued U.S. patent, two pending U.S. patent applications, and one pending provisional patent application and related worldwide patent application, that relate to ZGN-1258.

As of March 1, 2019, we own two pending U.S. patent applications, and related worldwide patent applications, and two pending PCT patent applications that relate to ZGN-1345.

As of March 1, 2019, we own twenty-one issued U.S. patents, and three pending U.S. patent applications with pending foreign counterpart applications and three pending U.S. provisional patent applications, all of which relate to our internal efforts to discover novel MetAP2 inhibitors.

We cannot provide any assurances that any of our pending patent applications that mature into issued patents will include claims with a scope sufficient to protect ZGN-1061, ZGN-1258, ZGN-1345, and our other product candidates. Other parties have developed technologies that may be related or competitive to our approach and may have filed or may file patent applications and may have received or may receive patents that may overlap or conflict with our patent applications, either by claiming the same methods or formulations or by claiming subject matter that could dominate our patent position. The patent positions of biotechnology and pharmaceutical companies, including our patent position, involve complex legal and factual questions, and, therefore, the issuance, scope, validity and enforceability of any patent claims that we may obtain cannot be predicted with certainty. Patents, if issued, may be challenged, deemed unenforceable, invalidated, or circumvented. U.S. patents and patent applications may also be subject to interference proceedings, *ex parte* reexamination, or *inter partes* review proceedings, supplemental examination and challenges in district court. Patents may be subjected to opposition, post-grant review, or comparable proceedings lodged in various foreign, both national and regional, patent offices. These proceedings could result in either loss of the patent or denial of the patent application or loss or reduction in the scope of one or more of the claims of the patent or patent application. In addition, such proceedings may be costly. Thus, any patents that we may own or exclusively license may not provide any protection against competitors. Furthermore, an adverse decision in an interference proceeding can result in a third party receiving the patent right sought by us, which in turn could affect our ability to develop, market or otherwise commercialize ZGN-1061, ZGN-1258, ZGN-1345, and our other product candidates.

Furthermore, though an issued patent is presumed valid and enforceable, its issuance is not conclusive as to its validity or its enforceability and it may not provide us with adequate proprietary protection or competitive advantages against competitors with similar products. Competitors may also be able to design around our patents. Other parties may develop and obtain patent protection for more effective technologies, designs or methods. The laws of some foreign countries do not protect our proprietary rights to the same extent as the laws of the United States, and we may encounter significant problems in protecting our proprietary rights in these countries. If these developments were to occur, they could have a material adverse effect on our potential future sales.

Our ability to enforce our patent rights depends on our ability to detect infringement. It is difficult to detect infringers who do not advertise the components that are used in their products. Moreover, it may be difficult or impossible to obtain evidence of infringement in a competitor's or potential competitor's product. Any litigation to enforce or defend our patent rights, even if we were to prevail, could be costly and time-consuming and would divert the attention of our management and key personnel from our business operations. We may not prevail in any lawsuits that we initiate and the damages or other remedies awarded if we were to prevail may not be commercially meaningful.

In addition, proceedings to enforce or defend our patents could put our patents at risk of being invalidated, held unenforceable, or interpreted narrowly. Such proceedings could also provoke third parties to assert claims against us, including that some or all of the claims in one or more of our patents are invalid or otherwise unenforceable. If any of our patents covering ZGN-1061, ZGN-1258 or ZGN-1345, are invalidated or found unenforceable, our financial position and results of operations would be materially and adversely impacted. In addition, if a court found that valid, enforceable patents held by third parties covered ZGN-1061, ZGN-1258 or ZGN-1345, our financial position and results of operations would also be materially and adversely impacted.

The degree of future protection for our proprietary rights is uncertain, and we cannot ensure that:

- any of our patents, or any of our pending patent applications, if issued, will include claims having a scope sufficient to protect ZGN-1061, ZGN-1258, ZGN-1345 or any other products or product candidates;
- any of our pending patent applications will issue as patents;
- we will be able to successfully develop and commercialize ZGN-1061, ZGN-1258 or ZGN-1345, if approved, before our relevant patents expire;
- we were the first to make the inventions covered by each of our patents and pending patent applications;
- we were the first to file patent applications for these inventions;
- others will not develop similar or alternative technologies that do not infringe our patents;
- any of our patents will be found to ultimately be valid and enforceable;
- any patents issued to us will provide a basis for an exclusive market for our commercially viable products, will provide us with any competitive advantages or will not be challenged by third parties;
- we will develop additional proprietary technologies or product candidates that are separately patentable; or
- that our commercial activities or products will not infringe upon the patents of others.

We rely upon unpatented trade secrets, unpatented know-how and continuing technological innovation to develop and maintain our competitive position, which we seek to protect, in part, by confidentiality agreements with our employees and our collaborators and consultants. We also have agreements with our employees and selected consultants that obligate them to assign their inventions to us and have non-compete agreements with some, but not all, of our consultants. It is possible that technology relevant to our business will be independently developed by a person that is not a party to such an agreement. Furthermore, if the employees and consultants who are parties to these agreements breach or violate the terms of these agreements, we may not have adequate remedies for any such breach or violation, and we could lose our trade secrets through such breaches or violations. Further, our trade secrets could otherwise become known or be independently discovered by our competitors.

We may infringe the intellectual property rights of others, which may prevent or delay our product development efforts and stop us from commercializing or increase the costs of commercializing ZGN-1061 or our other product candidates, if approved.

Our success will depend in part on our ability to operate without infringing the intellectual property and proprietary rights of third parties. We cannot assure you that our business, products and methods do not or will not infringe the patents or other intellectual property rights of third parties.

The pharmaceutical industry is characterized by extensive litigation regarding patents and other intellectual property rights. Other parties may allege that ZGN-1061 or our other product candidates or the use of our technologies infringes patent claims or other intellectual property rights held by them or that we are employing their proprietary technology without authorization. Patent and other types of intellectual property litigation can involve complex factual and legal questions, and their outcome is uncertain. Any claim relating to intellectual property infringement that is successfully asserted against us

may require us to pay substantial damages, including treble damages and attorneys' fees if we are found to be willfully infringing another party's patents, for past use of the asserted intellectual property and royalties and other consideration going forward if we are forced to take a license. In addition, if any such claim were successfully asserted against us and we could not obtain such a license, we may be forced to stop or delay developing, manufacturing, selling or otherwise commercializing ZGN-1061 or our other product candidates.

Even if we are successful in these proceedings, we may incur substantial costs and divert management time and attention in pursuing these proceedings, which could have a material adverse effect on us. If we are unable to avoid infringing the patent rights of others, we may be required to seek a license, defend an infringement action or challenge the validity of the patents in court, or redesign our products. Patent litigation is costly and time consuming. We may not have sufficient resources to bring these actions to a successful conclusion. In addition, intellectual property litigation or claims could force us to do one or more of the following:

- cease developing, selling or otherwise commercializing ZGN-1061;
- cease preparations or developing or our other product candidates;
- pay substantial damages for past use of the asserted intellectual property;
- obtain a license from the holder of the asserted intellectual property, which license may not be available on reasonable terms, if at all; and
- in the case of trademark claims, redesign or rename the trademarks or trade names of our product candidates to avoid infringing the intellectual property rights of third parties, which may not be possible and, even if possible, could be costly and time-consuming.

Any of these risks coming to fruition could have a material adverse effect on our business, results of operations, financial condition and prospects.

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

We may also be subject to claims that former employees, collaborators or other third parties have an ownership interest in our patents or other intellectual property. Litigation may be necessary to defend against these and other claims challenging inventorship or ownership. If we fail in defending any such claims, in addition to paying monetary damages, we may lose valuable intellectual property rights, such as exclusive ownership of, or right to use, valuable intellectual property. Such an outcome could have a material adverse effect on our business. Even if we are successful in defending against such claims, litigation could result in substantial costs and be a distraction to management and other employees.

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

The U.S. Patent and Trademark Office, or U.S. PTO, and various foreign governmental patent agencies require compliance with a number of procedural, documentary, fee payment and other provisions during the patent process. There are situations in which noncompliance can result in abandonment or lapse of a patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. In such an event, competitors might be able to enter the market earlier than would otherwise have been the case.

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

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

Interference proceedings provoked by third parties or brought by us may be necessary to determine the priority of inventions with respect to our patents or patent applications or those of our licensors. An unfavorable outcome could require us to cease using the related technology or to attempt to license rights to it from the prevailing party. Our business could be

harmed if the prevailing party does not offer us a license on commercially reasonable terms. Our defense of litigation or interference proceedings may fail and, even if successful, may result in substantial costs and distract our management and other employees. We may not be able to prevent, alone or with our licensors, misappropriation of our intellectual property rights, particularly in countries where the laws may not protect those rights as fully as in the United States.

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

Issued patents covering our product candidates could be found invalid or unenforceable if challenged in court.

If we or one of our licensing partners initiated legal proceedings against a third party to enforce a patent covering our product candidate, the defendant could counterclaim that the patent covering our product candidate is invalid and/or unenforceable. In patent litigation in the United States, defendant counterclaims alleging invalidity and/or unenforceability are commonplace. Grounds for a validity challenge include alleged failures to meet any of several statutory requirements, including lack of novelty, obviousness or non-enablement. Grounds for unenforceability assertions include allegations that someone connected with prosecution of the patent withheld relevant information from the U.S. PTO, or made a misleading statement, during prosecution. Third parties may also raise similar claims before administrative bodies in the United States or abroad, even outside the context of litigation. Such mechanisms include re-examination, post grant review and equivalent proceedings in foreign jurisdictions, e.g., opposition proceedings. Such proceedings could result in revocation or amendment of our patents in such a way that they no longer cover our product candidates or competitive products. The outcome following legal assertions of invalidity and unenforceability is unpredictable. With respect to validity, for example, we cannot be certain that there is no invalidating prior act, of which we and the patent examiner were unaware during prosecution. If a defendant were to prevail on a legal assertion of invalidity and/or unenforceability, we would lose at least part, and perhaps all, of the patent protection on our product candidates. Such a loss of patent protection would have a material adverse impact on our business.

We do not seek to protect our intellectual property rights in all jurisdictions throughout the world and we may not be able to adequately enforce our intellectual property rights even in the jurisdictions where we seek protection.

Filing, prosecuting and defending patents on product candidates in all countries and jurisdictions throughout the world would be prohibitively expensive, and our intellectual property rights in some countries outside the United States could be 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 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 our technologies in jurisdictions where we have not obtained patent protection to develop their own products and further, may export otherwise infringing products to territories where we have patent protection, but enforcement is not as strong as that in the United States. These products may compete with our products and our patents or other intellectual property rights may not be effective or sufficient to prevent them from competing.

Many companies have encountered significant problems in protecting and defending intellectual property rights in foreign jurisdictions. The legal systems of certain countries, particularly certain developing countries, do not favor the enforcement of patents and other intellectual property protection, particularly those relating to biopharmaceuticals, which could make it difficult for us to stop the infringement of our patents or marketing of competing products in violation of our proprietary rights generally. For example, an April 2014 report from the Office of the United States Trade Representative identified a number of countries, including India and China, where challenges to the procurement and enforcement of patent rights have been reported. Several countries, including India and China, have been listed in the report every year since 1989. Proceedings to enforce our patent rights in foreign jurisdictions could result in substantial costs and divert our efforts and attention from other aspects of our business, could put our patents at risk of being invalidated or interpreted narrowly, could put our patent applications at risk of not issuing and could provoke third parties to assert claims against us. We may not prevail in any lawsuits that we initiate and the damages or other remedies awarded, if any, may not be commercially meaningful. Accordingly, our efforts to enforce our intellectual property rights around the world may be inadequate to obtain a significant commercial advantage from the intellectual property that we develop or license.

We are dependent on licensed intellectual property for certain early-stage product candidates. If we were to lose our rights to licensed intellectual property, we may not be able to continue developing or commercializing such product candidates, if approved.

We have an exclusive license with Children's Medical Center Corporation, pursuant to which we exclusively licensed certain patent rights relating to decreasing the growth of fat tissue, on a worldwide basis. We may enter into additional licenses for third-party intellectual property that are necessary or useful to our business. Current or future licensors may also allege that we have breached our license agreement and may accordingly seek to terminate our license with them. In addition, current or future licensors may decide to terminate our license at will. If successful, this could result in our loss of the right to use the licensed intellectual property, which could materially adversely affect our ability to develop and commercialize a product candidate or product, if approved, as well as harm our competitive business position and our business prospects.

We have not yet registered trademarks for a commercial trade name for ZGN-1061 or our other product candidates and failure to secure such registrations could adversely affect our business.

We have not yet registered trademarks for a commercial trade name for ZGN-1061 or our other product candidates. Any future trademark applications may be rejected during trademark registration proceedings. Although we would be given an opportunity to respond to those rejections, we may be unable to overcome such rejections. In addition, in the U.S. PTO and in comparable agencies in many foreign jurisdictions, third parties are given an opportunity to oppose pending trademark applications and to seek to cancel registered trademarks. Opposition or cancellation proceedings may be filed against our trademarks, and our trademarks may not survive such proceedings. Moreover, any name we propose to use with our product candidates in the United States must be approved by the FDA, regardless of whether we have registered it, or applied to register it, as a trademark. The FDA typically conducts a review of proposed product names, including an evaluation of potential for confusion with other product names. If the FDA objects to any of our proposed proprietary product names, we may be required to expend significant additional resources in an effort to identify a suitable substitute name that would qualify under applicable trademark laws, not infringe the existing rights of third parties and be acceptable to the FDA.

If we do not obtain additional protection under the Hatch-Waxman Amendments and similar foreign legislation by extending the patent terms and obtaining data exclusivity for ZGN-1061, our business may be materially harmed.

Depending upon the timing, duration and specifics of development and FDA marketing approval of ZGN-1061 or our other product candidates, one or more of our U.S. patents may be eligible for limited patent term restoration under the Drug Price Competition and Patent Term Restoration Act of 1984, referred to as the Hatch-Waxman Amendments. The Hatch-Waxman Amendments permit a patent restoration term of up to five years as compensation for patent term lost during product development and the FDA regulatory review process. However, we may not be granted an extension because of, for example, failing to apply within applicable deadlines, failing to apply prior to expiration of relevant patents or otherwise failing to satisfy applicable requirements. Moreover, the applicable time period or the scope of patent protection afforded could be less than we request. If we are unable to obtain patent term extension or restoration or the term of any such extension is less than we request, our competitors may obtain approval of competing products following our patent expiration, and our ability to generate revenues could be materially adversely affected.

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

As is the case with other biopharmaceutical companies, our success is heavily dependent on intellectual property, particularly patents. Obtaining and enforcing patents in the biopharmaceutical industry involves both technological and legal complexity and is therefore costly, time consuming and inherently uncertain. Changes in either the patent laws or interpretation of the patent laws in the United States could increase the uncertainties and costs surrounding the prosecution of patent applications and the enforcement or defense of issued patents. Patent reform legislation in the United States and other countries, including the Leahy-Smith America Invents Act, or the Leahy-Smith Act, signed into law in September 2011, could increase those uncertainties and costs. The Leahy-Smith Act includes a number of significant changes to U.S. patent law. These include provisions that affect the way patent applications are prosecuted, redefine prior art and provide more efficient and cost-effective avenues for competitors to challenge the validity of patents. For example, the Leahy-Smith Act allows third-party submission of prior art to the U.S. PTO during patent prosecution and additional procedures to attack the validity of a patent by U.S. PTO administered post-grant proceedings, including post-grant review, inter partes review, and derivation proceedings. In addition, the Leahy-Smith Act has transformed the U.S. patent system from a "first-to-invent" system to a "first-to-file" system in which, assuming that other requirements for patentability are met, the first inventor to file a patent application will be entitled to the patent on an invention regardless of whether a third party was the first to invent the claimed invention. The first-to-file provisions, however, only became effective on March 16, 2013. Accordingly, it is not yet

clear what, if any, impact the Leahy-Smith Act will have on the operation of our business. However, the Leahy-Smith Act and its implementation could make it more difficult to obtain patent protection for our inventions and increase the uncertainties and costs surrounding the prosecution of our or our collaboration partners' patent applications and the enforcement or defense of our or our collaboration partners' issued patents, all of which could harm our business, results of operations, financial condition and prospects.

The U.S. Supreme Court has ruled on several patent cases in recent years, either narrowing the scope of patent protection available in certain circumstances or weakening the rights of patent owners in certain situations. Additionally, there have been recent proposals for additional changes to the patent laws of the United States and other countries that, if adopted, could impact our ability to enforce our proprietary technology. Depending on future actions by the U.S. Congress, the U.S. courts, the U.S. PTO and the relevant law-making bodies in other countries, the laws and regulations governing patents could change in unpredictable ways that would weaken our ability to obtain new patents or to enforce our existing patents and patents that we might obtain in the future.

We may be subject to damages resulting from claims that we or our employees have wrongfully used or disclosed alleged trade secrets of their former employers.

Our employees have been previously employed at other biotechnology or pharmaceutical companies, including our competitors or potential competitors. Although we are not aware of any claims currently pending against us, we may be subject to claims that these employees or we have inadvertently or otherwise used or disclosed trade secrets or other proprietary information of the former employers of our employees. Litigation may be necessary to defend against these claims. Even if we are successful in defending against these claims, litigation could result in substantial costs and be a distraction to management. If we fail in defending such claims, in addition to paying money claims, we may lose valuable intellectual property rights or personnel. A loss of key personnel or their work product could hamper or prevent our ability to develop and commercialize ZGN-1061 or our other product candidates, which would materially adversely affect our business, financial condition and results of operations.

General Company-Related Risks

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

Our success depends upon the principal members of our executive, medical and development teams, the loss of whose services may adversely impact the achievement of our research, development or commercialization objectives. We have entered into a severance and change in control agreement with our executive officers and department vice president level employees, but they may terminate their employment with us at any time. We also do not have any key-man life insurance on any of our executive officers or employees.

With any change in leadership, there is also a risk to retention of employees, as well as the potential for disruption to business operations, initiatives, plans and strategies.

We also rely on consultants and advisors, including scientific and clinical advisors, to assist us in formulating our development and commercialization strategy. Our consultants and advisors may be employed by employers other than us and may have commitments under consulting or advisory contracts with other entities that may limit their availability to us and may not be subject to our standard non-compete agreements. Recruiting and retaining qualified scientific personnel and sales and marketing personnel will also be critical to our success. We may not be able to attract and retain these personnel on acceptable terms given the workforce reduction and competition among numerous pharmaceutical and biotechnology companies for similar personnel. We also experience competition for the hiring of scientific personnel from universities and research institutions. Failure to succeed in clinical trials may make it more challenging to recruit and retain qualified scientific personnel.

Our employees may engage in misconduct or other improper activities, including violating applicable regulatory standards and requirements or engaging in insider trading, which could significantly harm our business.

We are exposed to the risk of employee fraud or other misconduct. Misconduct by employees could include intentional failures to comply with the regulations of the FDA and applicable non-U.S. regulators, provide accurate information to the FDA and applicable non-U.S. regulators, comply with healthcare fraud and abuse laws and regulations in the United States and abroad, report financial information or data accurately or disclose unauthorized activities to us. In particular, sales, marketing and business arrangements in the healthcare industry are subject to extensive laws and regulations intended to

prevent fraud, misconduct, kickbacks, self-dealing and other abusive practices. These laws and regulations restrict or prohibit a wide range of pricing, discounting, marketing and promotion, sales commission, customer incentive programs and other business arrangements. Employee misconduct could also involve the improper use of, including trading on, information obtained in the course of clinical trials, which could result in regulatory sanctions and serious harm to our reputation. We have adopted an insider trading policy and a code of conduct, but it is not always possible to identify and deter employee misconduct, and the precautions we take to detect and prevent this activity may be ineffective in controlling unknown or unmanaged risks or losses or in protecting us from governmental investigations or other actions or lawsuits stemming from a failure to comply with these laws or regulations. If any such actions are instituted against us, and we are not successful in defending ourselves or asserting our rights, those actions could have a significant impact on our business, including the imposition of significant fines or other sanctions.

We face potential product liability exposure, and, if claims are brought against us, we may incur substantial liability.

The use of ZGN-1061 and our other product candidates in clinical trials, if any, and the sale of ZGN-1061 and our other product candidates, if developed and approved, exposes us to the risk of product liability claims. Product liability claims might be brought against us by patients, healthcare providers or others selling or otherwise coming into contact with ZGN-1061 or our other product candidates. For example, we may be sued if any product we develop allegedly causes injury or death or is found to be otherwise unsuitable during product testing, manufacturing, marketing or sale. Any such product liability claims may include allegations of defects in manufacturing, defects in design, a failure to warn of dangers inherent in the product, including as a result of interactions with alcohol or other drugs, negligence, strict liability and a breach of warranties. Claims could also be asserted under state consumer protection acts. If we become subject to product liability claims and cannot successfully defend ourselves against them, we could incur substantial liabilities. In addition, regardless of merit or eventual outcome, product liability claims may result in, among other things:

- withdrawal of patients from our clinical trials;
- substantial monetary awards to patients or other claimants;
- decreased demand for ZGN-1061 or our other product candidates following marketing approval, if obtained;
- damage to our reputation and exposure to adverse publicity;
- increased FDA warnings on product labels;
- litigation costs;
- distraction of management's attention from our primary business;
- loss of revenue; and
- the inability to successfully commercialize ZGN-1061 or our other product candidates, if approved.

We maintain product liability insurance coverage for our clinical trials with a $10.0 million annual aggregate coverage limit. Nevertheless, our insurance coverage may be insufficient to reimburse us for any expenses or losses we may suffer. Moreover, in the future, we may not be able to maintain insurance coverage at a reasonable cost or in sufficient amounts to protect us against losses, including if insurance coverage becomes increasingly expensive. If and when we obtain marketing approval for ZGN-1061 or our other product candidates, we intend to expand our insurance coverage to include the sale of commercial products; however, we may not be able to obtain this product liability insurance on commercially reasonable terms. Large judgments have been awarded in class action lawsuits based on drugs that had unanticipated side effects. The cost of any product liability litigation or other proceedings, even if resolved in our favor, could be substantial, particularly in light of the size of our business and financial resources. A product liability claim or series of claims brought against us could cause our stock price to decline and, if we are unsuccessful in defending such a claim or claims and the resulting judgments exceed our insurance coverage, our financial condition, business and prospects could be materially adversely affected.

We must maintain effective internal control over financial reporting, and if we are unable to do so, the accuracy and timeliness of our financial reporting may be adversely affected, which could have a material adverse effect on our business and stock price.

We currently are an "emerging growth company," as defined in the Jumpstart our Business Startups Act of 2012, or the JOBS Act, and we have taken advantage of certain exemptions from various reporting requirements that are applicable to other public companies that are not "emerging growth companies" including not being required to comply with the auditor attestation requirements of Section 404(b) of the Sarbanes-Oxley Act.

We must maintain effective internal control over financial reporting in order to accurately and timely report our results of operations and financial condition. In addition, as a public company, the Sarbanes-Oxley Act of 2002, or the Sarbanes-Oxley Act, requires, among other things, that we assess the effectiveness of our disclosure controls and procedures quarterly and the effectiveness of our internal control over financial reporting at the end of each fiscal year.

The rules governing the standards that must be met for our management to assess our internal control over financial reporting pursuant to Section 404 of the Sarbanes-Oxley Act are complex and require significant documentation, testing and possible remediation. These stringent standards require that our audit committee be advised and regularly updated on management's review of internal control over financial reporting. Our management may not be able to effectively and timely implement controls and procedures that adequately respond to the increased regulatory compliance and reporting requirements that are applicable to us as a public company. If we fail to staff our accounting, finance and information technology functions adequately or maintain internal control over financial reporting adequate to meet the demands that will be placed upon us as a public company, including the requirements of the Sarbanes-Oxley Act, our business and reputation may be harmed and our stock price may decline. Furthermore, investor perceptions of us may be adversely affected, which could cause a decline in the market price of our common stock.

Comprehensive tax reform legislation could adversely affect our business and financial condition.

On December 22, 2017, President Trump signed into law the "Tax Cuts and Jobs Act," or the TCJA, that significantly reforms the Internal Revenue Code of 1986, as amended, or the Code. The TCJA, among other things, contains significant changes to corporate taxation, including reduction of the corporate tax rate, limitation of the tax deduction for interest expense, limitation of the deduction for net operating losses and elimination of net operating loss carrybacks and modifying or repealing many business deductions and credits (including reducing the business tax credit for certain clinical testing expenses incurred in the testing of certain drugs for rare diseases or conditions generally referred to as "orphan drugs"). Our net deferred tax assets and liabilities were revalued at the newly enacted U.S. corporate rate.

Our ability to use our net operating loss carryforwards and certain tax credit carryforwards may be subject to limitation.

Since our inception in 2005, we have not recorded any U.S. federal or state income tax benefits for the net losses we have incurred in each year or our earned tax credits, due to our uncertainty of realizing a benefit from those items. As of December 31, 2018, we had net operating loss carryforwards for federal and state income tax purposes of $55.7 million and $48.0 million, respectively, which begin to expire in 2026 and 2030, respectively. As of December 31, 2018, we also had available tax credit carryforwards for federal and state income tax purposes of $16.6 million and $3.4 million, respectively, which begin to expire in 2026 and 2022, respectively. Under Section 382 of the Code, changes in our ownership may limit the amount of our net operating loss carryforwards and tax credit carryforwards that could be utilized annually to offset our future taxable income, if any. This limitation would generally apply in the event of a cumulative change in ownership of our company of more than 50% within a three-year period. Any such limitation may significantly reduce our ability to utilize our net operating loss carryforwards and tax credit carryforwards before they expire. Our follow-on public offering, initial public offering, or IPO, private placements and other transactions that have occurred since our inception, may trigger such an ownership change pursuant to Section 382. Any such limitation, whether as the result of our follow-on public offering, IPO, prior private placements, sales of our common stock by our existing stockholders or additional sales of our common stock by us, could have a material adverse effect on our results of operations in future years. We have not completed a study to assess whether an ownership change for purposes of Section 382 has occurred, or whether there have been multiple ownership changes since our inception, due to the significant costs and complexities associated with such study. The reduction of the corporate tax rate under TCJA may cause a reduction in the economic benefit of our net operating loss carryforwards and other deferred tax assets available to us. Under the TCJA, net operating losses generated after December 31, 2017 will not be subject to expiration. As of December 31, 2018, we had net operating loss carryforwards that were generated after December 31, 2017, of $9.5 million that do not expire.

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

Our results of operations could be adversely affected by general conditions in the global economy and in the global financial markets. A severe or prolonged economic downturn could result in a variety of risks to our business, including, weakened demand for our product candidates and our ability to raise additional capital when needed on acceptable terms, if at all. A weak or declining economy could also strain our suppliers, possibly resulting in supply disruption, or cause our customers to delay making payments for our services. Any of the foregoing could harm our business and we cannot anticipate all of the ways in which the current economic climate and financial market conditions could adversely impact our business.

Our internal computer systems, or those of our third-party CROs or other contractors or consultants, may fail or suffer security breaches, which could result in a material disruption of our ZGN-1061, ZGN-1258, ZGN-1345 or other product candidate development programs.

Despite the implementation of security measures, our internal computer systems and those of our third-party CROs and other contractors and consultants are vulnerable to damage from computer viruses, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. While we have not experienced any such system failure or accident, if such an event were to occur and cause interruptions in our operations, it could result in a material disruption of our programs. For example, the loss of clinical trial data for ZGN-1061 could result in delays in our regulatory approval efforts and significantly increase our costs to recover or reproduce the data. To the extent that any disruption or security breach results in a loss of 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 ZGN-1061 could be delayed.

We may not be successful in our efforts to identify or discover additional product candidates.

The success of our business depends primarily upon our ability to identify, develop and commercialize products based on our MetAP2 platform. Although our product candidates are in the nonclinical and clinical development stage, our research programs may fail to identify other potential product candidates for clinical development for a number of reasons. Our research methodology may be unsuccessful in identifying potential product candidates or our potential product candidates may be shown to have harmful side effects or may have other characteristics that may make the products unmarketable or unlikely to receive marketing approval.

If any of these events occur, we may be forced to abandon our development efforts for a program or programs, which would have a material adverse effect on our business and could potentially cause us to cease operations. Research programs to identify new product candidates require substantial technical, financial and human resources. We may focus our efforts and resources on potential programs or product candidates that ultimately prove to be unsuccessful.

We may seek to establish collaborations and, if we are not able to establish them on commercially reasonable terms, we may have to alter our development and commercialization plans or expand our internal efforts and growth.

Our drug development programs and the potential commercialization of our product candidates will require substantial additional cash to fund expenses. For some of our product candidates, such as ZGN-1061, we may decide to collaborate with pharmaceutical and biotechnology companies for the development and potential commercialization of those product candidates in some or all markets.

We face significant competition in seeking appropriate collaborators. Whether we reach a definitive agreement for a collaboration for ZGN-1061 or our other product candidates will depend, among other things, upon our assessment of the collaborator's resources and expertise, the terms and conditions of the proposed collaboration and the proposed collaborator's evaluation of a number of factors, and whether we are able to resolve the clinical hold on ZGN-1061. Those factors may include the design or results of clinical trials, the likelihood of approval by the FDA or similar regulatory authorities outside the United States, the potential market for the applicable product candidate, the costs and complexities of manufacturing and delivering such product candidate to patients, the potential of competing products, the existence of uncertainty with respect to our ownership of technology, which can exist if there is a challenge to such ownership without regard to the merits of the challenge and industry and market conditions generally. The collaborator may also consider alternative product candidates or technologies for similar indications that may be available to collaborate on and whether such collaboration could be more attractive than the one with us for our product candidate. The terms of any collaboration or other arrangements that we may establish may not be favorable to us.

We may also be restricted under existing license agreements from entering into future agreements on certain terms with potential collaborators. Collaborations are complex and time-consuming to negotiate and document. In addition, there have been a significant number of recent business combinations among large pharmaceutical companies that have resulted in a reduced number of potential future collaborators.

We may not be able to negotiate collaborations on a timely basis, on acceptable terms, or at all. If we are unable or unwilling to do so, we may have to curtail the development of ZGN-1061 or our other product candidates for which we are seeking to collaborate, reduce or delay its development program or one or more of our other development programs, delay potential commercialization in some or all markets or reduce the scope of any sales or marketing activities, or increase our expenditures and undertake development or commercialization activities at our own expense, including potentially increasing

our infrastructure and investment outside the United States. If we elect to increase our expenditures to fund development or commercialization activities on our own, we will need to obtain additional capital, which may not be available to us on acceptable terms or at all. If we do not have sufficient funds, we may not be able to further develop our product candidates or bring them to market and generate product revenue. In addition, such efforts may require diversion of a disproportionate amount of our attention away from other day-to-day activities and require devotion of a substantial amount of our time to managing these expansion activities.

In addition, any future collaborations that we enter into for ZGN-1061 or our other product candidates may not be successful. The success of our collaboration arrangements will depend heavily on the efforts and activities of our collaborators. Collaborators generally have significant discretion in determining the efforts and resources that they will apply to these collaborations. Disagreements between parties to a collaboration arrangement regarding clinical development and commercialization matters can lead to delays in the development process or commercializing the applicable product candidate and, in some cases, termination of the collaboration arrangement. These disagreements can be difficult to resolve if neither of the parties has final decision-making authority. Collaborations with pharmaceutical or biotechnology companies and other third parties often are terminated or allowed to expire by the other party. Any such termination or expiration would adversely affect us financially and could harm our business reputation.

We may acquire businesses or products, or form strategic alliances, in the future, and we may not realize the benefits of such acquisitions or alliances.

We may acquire additional businesses or products, form strategic alliances or create joint ventures with third parties that we believe will complement or augment our existing business. If we acquire businesses with promising markets or technologies, we may not be able to realize the benefit of such transactions if we are unable to successfully integrate such businesses with our existing operations and company culture. We may encounter numerous difficulties in developing, manufacturing and marketing any new products resulting from a strategic alliance or acquisition that delay or prevent us from realizing their expected benefits or enhancing our business. We cannot assure you that, following any such transaction, we will achieve the expected synergies to justify the transaction.

Risks Related to Our Financial Position and Need for Capital

We have not generated any revenue from product sales. We have incurred significant operating losses since our inception and anticipate that we will incur continued losses for the foreseeable future.

Biopharmaceutical product development is a highly speculative undertaking and involves a substantial degree of risk. Our operations to date have been limited primarily to organizing and staffing our company and conducting research and development activities for ZGN-1061, ZGN-1258, ZGN-1345, beloranib, ZGN-839 and additional MetAP2 inhibitors. We have never generated any revenue from product sales. We have not obtained regulatory approvals for any of our product candidates.

Since our inception and until July 2016, we focused substantially all of our efforts and financial resources on developing beloranib, which was in Phase 3 clinical development for our lead indication of the treatment of hyperphagia and obesity in patients with PWS and Phase 2 clinical development for the treatment of obesity in patients with hypothalamic injury-associated obesity, or HIAO. In December 2015, the FDA put the beloranib IND application on full clinical hold. Due to the uncertainties, costs and risks associated with the development of beloranib, in July 2016, we suspended further development of beloranib and directed our efforts and financial resources to developing ZGN-1061. In October 2016, we suspended our development of ZGN-839 in order to focus all of our resources to developing ZGN-1061 and the discovery and development of novel and highly differentiated MetAP2 inhibitors. In early 2018, we announced that we are returning to the rare metabolic disease space with a second highly optimized MetAP2 development candidate, ZGN-1258, targeting an initial indication of PWS. In March 2019, we suspended our plans to file an IND for ZGN-1258 in order to evaluate ZGN-1258 following an unexpected finding in muscle tissue in rodent toxicology studies.

We have funded our operations to date through proceeds from sales of redeemable convertible preferred stock, convertible debt and proceeds from our IPO and follow-on public offerings, and have incurred losses in each year since our inception. In July 2018, we sold 9,200,000 shares of our common stock at a price of $7.50 per share. Our net losses were $61.4 million for the year ended December 31, 2018 and $52.0 million for the year ended December 31, 2017. As of December 31, 2018, we had an accumulated deficit of $350.9 million. Substantially all of our operating losses resulted from costs incurred in connection with our development programs for ZGN-1061, ZGN-1258, ZGN-1345, beloranib, ZGN-839, early research activities, licensing milestone fees and from general and administrative costs associated with our operations. We expect to incur increasing levels of operating losses over the next several years and for the foreseeable future. Our prior

losses, combined with expected future losses, have had and will continue to have an adverse effect on our stockholders' equity and working capital. We expect our research and development expenses will increase over time in connection with our expected clinical development of ZGN-1061, ZGN-1258 (if our further evaluation of ZGN-1258 warrants continued development), and of any other product candidates we may choose to pursue, including ZGN-1345. In addition, if and when we obtain marketing approval for ZGN-1061, ZGN-1258 (if our further evaluation of ZGN-1258 warrants continued development and commercialization) or ZGN-1345 we will incur significant sales, marketing and outsourced manufacturing expenses. We will continue to incur additional costs associated with operating as a public company. As a result, we expect to continue to incur significant operating losses that would increase over time for the foreseeable future. Because of the numerous risks and uncertainties associated with developing pharmaceutical products, we are unable to predict the extent of any future losses or when we will become profitable, if at all. Even if we do become profitable, we may not be able to sustain or increase our profitability on a quarterly or annual basis.

Our ability to become profitable depends upon our ability to generate revenue. To date, we have not generated any revenue from any of our product candidates, and we do not know when, or if, we will generate any revenue. We do not expect to generate significant revenue unless and until we obtain marketing approval of, and begin to sell, our product candidates. Our ability to generate revenue depends on a number of factors, including, but not limited to, our ability to:

- initiate and successfully complete clinical trials that meet their clinical endpoints;
- successfully submit IND applications and obtain FDA approval to initiate clinical trials for ZGN-1061, ZGN-1258 (if our further evaluation warrants continued development of ZGN-1258) and ZGN-1345;
- initiate and successfully complete all safety studies required to obtain U.S. and foreign marketing approval for ZGN-1061 in the indications we are pursuing;
- commercialize our product candidates, if developed and approved, by developing a sales force or entering into collaborations with third parties; and
- achieve market acceptance of our product candidates in the medical community and with third-party payors.

Absent our entering into a collaboration or partnership agreement, we expect to incur significant sales and marketing costs when we prepare to commercialize our product candidates. Even if we initiate and successfully complete our clinical trials of our product candidates, and our product candidates are approved for commercial sale, and despite expending these costs, our product candidates may not be commercially successful drugs. We may not achieve profitability soon after generating product sales, if ever. If we are unable to generate sufficient product revenue, we will not become profitable and may be unable to continue operations without continued funding.

We will need to raise additional funding, which may not be available on acceptable terms, or at all. Failure to obtain this necessary capital when needed may force us to delay, limit or terminate our product development efforts or other operations.

Developing small molecule products is expensive, and we expect our research and development expenses to increase substantially in connection with our ongoing activities, particularly as we advance ZGN-1061 into later stage clinical trials and as we continue our preparations for receiving IND allowances for ZGN-1061, ZGN-1258 (if our further evaluation of ZGN-1258 warrants continued preparations) and ZGN-1345 with the FDA and advance ZGN-1258 (if our further evaluation of ZGN-1258 warrants advancement) and ZGN-1345 into the clinical trial stage. Depending on the status of regulatory approval or, if approved, commercialization of ZGN-1061, ZGN-1258 (if our further evaluation of ZGN-1258 warrants continued development and commercialization), ZGN-1345 or any of our other product candidates, as well as the progress we make in selling ZGN-1061, ZGN-1258, ZGN-1345 or any of our other product candidates, we will require additional capital to fund operating needs thereafter. We may also need to raise additional funds sooner if we choose to pursue additional indications and/or geographies for ZGN-1061, ZGN-1258, ZGN-1345, or our other product candidates or otherwise expand more rapidly than we presently anticipate.

As of December 31, 2018, our cash, cash equivalents and marketable securities were $118.1 million. We expect that our cash, cash equivalents and marketable securities will be sufficient to fund our current operations for a period of at least one year from the issuance date of this Annual Report. However, our operating plan may change as a result of many factors currently unknown to us, and we may need to seek additional funds sooner than planned, through public or private equity or debt financings, government or other third-party funding, marketing and distribution arrangements and other collaborations, strategic alliances and licensing arrangements or a combination of these approaches. In any event, we will require additional capital to obtain regulatory approval for, and to commercialize, our product candidates. Raising funds in the current economic environment may present additional challenges. Even if we believe we have sufficient funds for our current or

future operating plans, we may seek additional capital if market conditions are favorable or if we have specific strategic considerations.

Any additional fundraising efforts may divert our management from their day-to-day activities, which may adversely affect our ability to develop and commercialize our product candidates. In addition, we cannot guarantee that future financing will be available in sufficient amounts or on terms acceptable to us, if at all. Moreover, the terms of any financing may adversely affect the holdings or the rights of our stockholders and the issuance of additional securities, whether equity or debt, by us, or the possibility of such issuance, may cause the market price of our shares to decline. The sale of additional equity or convertible securities would dilute all of our stockholders. The incurrence of indebtedness would result in increased fixed payment obligations and we may be required to agree to certain restrictive covenants, 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. We could also be required to seek funds through arrangements with collaborative partners or otherwise at an earlier stage than otherwise would be desirable and we may be required to relinquish rights to some of our technologies or product candidate or otherwise agree to terms unfavorable to us, any of which may have a material adverse effect on our business, operating results and prospects.

If we are unable to obtain funding on a timely basis, we may be required to significantly curtail, delay or discontinue one or more of our research or development programs or the commercialization of any product candidate or be unable to expand our operations or otherwise capitalize on our business opportunities, as desired, which could materially affect our business, financial condition and results of operations.

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

We may seek additional capital through a combination of private and public equity offerings, debt financings, collaborations and strategic and licensing arrangements. On July 2, 2018, we completed a public offering of our common stock, which resulted in the sale of 9,200,000 shares at a price of $7.50 per share, resulting in net proceeds of approximately $64.6 million after deducting underwriting discounts and commissions, as well as offering costs. On November 9, 2018, we entered into a sales agreement, or the Sales Agreement, with Cowen and Company, LLC, or Cowen, to sell shares of our common stock, with aggregate gross sales proceeds of up to $50.0 million, from time to time, through an at-the-market equity offering program under which Cowen will act as its sales agent. Through December 31, 2018 we have not sold any shares under the Sales Agreement. To the extent that we raise additional capital through the sale of common stock or securities convertible or exchangeable into common stock, a stockholder's ownership interest in our company will be diluted. In addition, the terms of any such securities may include liquidation or other preferences that materially adversely affect the rights of our stockholders. Debt financing, if available, would increase our fixed payment obligations and may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or declaring dividends. If we raise additional funds through collaboration, strategic partnerships and licensing arrangements with third parties, we may have to relinquish valuable rights to ZGN-1061 or our other product candidates, our intellectual property, future revenue streams or grant licenses on terms that are not favorable to us.

Risks Related to Our Common Stock

We expect that our stock price will continue to fluctuate significantly.

The market price of shares of our common stock, similar to the market price of shares of common stock of other biopharmaceutical companies, is subject to wide fluctuations. From January 1, 2018 to December 31, 2018 the daily closing price of our common stock on the NASDAQ Global Market ranged from a high of $12.04 to a low of $4.77 and will continue to be subject to wide fluctuations in response to many risk factors listed in this section, and others beyond our control, including:

- plans for, progress of, or results from nonclinical studies and clinical trials of ZGN-1061 and/or our other product candidates;
- the failure of the FDA to grant an IND allowance for ZGN-1061 or our other product candidates;
- the failure of the FDA or the EMA to approve ZGN-1061 or our other product candidates;
- our ability to establish an adequate safety margin and profile for ZGN-1061 or our other product candidates, including risk of serious thromboembolic events;

- announcements of new products, technologies, commercial relationships, acquisitions or other events by us or our competitors;
- the success or failure of other type 2 diabetes or PWS therapies;
- regulatory or legal developments in the United States and other countries;
- failure of ZGN-1061, or our other product candidates, if successfully developed and approved, to achieve commercial success;
- our ability to continue to evaluate ZGN-1258 following an unexpected finding in rodent toxicology studies;
- fluctuations in stock market prices and trading volumes of similar companies;
- general market conditions and overall fluctuations in U.S. equity markets;
- variations in our quarterly operating results;
- changes in our financial guidance or securities analysts' estimates of our financial performance;
- changes in accounting principles;
- our ability to raise additional capital and the terms on which we can raise it;
- sales of large blocks of our common stock, including sales by our executive officers, directors and significant stockholders;
- additions or departures of key personnel;
- discussion of us or our stock price by the press and by online investor communities; and
- other risks and uncertainties described in these risk factors.

These and other market and industry factors may cause the market price and demand for our common stock to fluctuate substantially, regardless of our actual operating performance, which may limit or prevent investors from readily selling their shares of common stock and may otherwise negatively affect the liquidity of our common stock. In addition, the stock market in general, and NASDAQ listed and biopharmaceutical companies in particular, have experienced extreme price and volume fluctuations that have often been unrelated or disproportionate to the operating performance of these companies. In the past, when the market price of a stock has been volatile, holders of that stock have instituted securities class action litigation against the company that issued the stock.

Our executive officers, directors, and principal stockholders exercise significant control over our company.

As of March 1, 2019, the existing holdings of our executive officers, directors, principal stockholders and their affiliates, including investment funds affiliated with Atlas Ventures, entities affiliated with Fidelity Investment, entities affiliated with BlackRock, Inc. and Great Point Partners, LLC, represent beneficial ownership, in the aggregate, of approximately 36.4% of our common stock. As a result, these stockholders, if they act together, are able to influence our management and affairs and control the outcome of matters submitted to our stockholders for approval, including the election of directors and any sale, merger, consolidation, or sale of all or substantially all of our assets. The concentration of voting power among these stockholders may have an adverse effect on the price of our common stock. In addition, this concentration of ownership might adversely affect the market price of our common stock by:

- delaying, deferring or preventing a change of control of us;
- impeding a merger, consolidation, takeover or other business combination involving us; or
- discouraging a potential acquirer from making a tender offer or otherwise attempting to obtain control of us.

Future sales of our common stock may cause our stock price to decline.

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

We may be at an increased risk of securities class action litigation.

Historically, securities class action litigation has often been brought against a company following a decline in the market price of its securities. This risk is especially relevant for us because biotechnology and pharmaceutical companies have experienced significant stock price volatility in recent years.

We are an "emerging growth company" and a "smaller reporting company" and have availed ourselves of reduced disclosure requirements applicable to emerging growth companies and smaller reporting companies, which could make our common stock less attractive to investors.

We are an "emerging growth company," as defined in the JOBS Act, and we have taken advantage of certain exemptions from various reporting requirements that are applicable to other public companies that are not "emerging growth companies" including not being required to comply with the auditor attestation requirements of Section 404(b) of the Sarbanes-Oxley Act, reduced disclosure obligations regarding executive compensation in our periodic reports and proxy statements, and exemptions from the requirements of holding a nonbinding advisory vote on executive compensation and shareholder approval of any golden parachute payments not previously approved. In addition, Section 107 of the JOBS Act also provides that an emerging growth company can take advantage of the extended transition period provided in Section 7(a)(2)(B) of the Securities Act, for complying with new or revised accounting standards. In other words, an emerging growth company can delay the adoption of certain accounting standards until those standards would otherwise apply to private companies. However, we are electing not to take advantage of such extended transition period, and as a result we will comply with new or revised accounting standards on the relevant dates on which adoption of such standards is required for non-emerging growth companies. Section 107 of the JOBS Act provides that our decision to not take advantage of the extended transition period for complying with new or revised accounting standards is irrevocable. We cannot predict if investors will find our common stock less attractive because we may rely on any of the exemptions available under the JOBS Act. If some investors find our common stock less attractive as a result, there may be a less active trading market for our common stock and our stock price may be more volatile. We may take advantage of these reporting exemptions until we are no longer an emerging growth company. We will remain an emerging growth company until the earliest of (i) the last day of the fiscal year in which we have total annual gross revenue of $1.07 billion or more; (ii) December 31, 2019; (iii) the date on which we have issued more than $1.07 billion in nonconvertible debt during the previous three years; and (iv) the date on which we are deemed to be a large accelerated filer under the rules of the SEC.

We are also a smaller reporting company, and we will remain a smaller reporting company as long as our voting and non-voting common shares held by non-affiliates is less than $250 million measured on the last business day of our second fiscal quarter, or our annual revenues are less than $100 million during the most recently completed fiscal year and our voting and non-voting common shares held by non-affiliates is less than $700 million measured on the last business day of our second fiscal quarter. Similar to emerging growth companies, smaller reporting companies are able to provide simplified executive compensation disclosure and have certain other reduced disclosure obligations, including, among other things, being required to provide only two years of audited financial statements and not being required to provide selected financial data, supplemental financial information or risk factors.

We may choose to take advantage of some, but not all, of the available exemptions for emerging growth companies and smaller reporting companies. We cannot predict whether investors will find our common stock less attractive if we rely on these exemptions. If some investors find our common stock less attractive as a result, there may be a less active trading market for our common stock and our shares price may be more volatile.

We have never paid dividends on our common stock and we do not anticipate paying any dividends in the foreseeable future. Consequently, any gains from an investment in our common stock will likely depend on whether the price of our common stock increases.

We have not paid dividends on any of our common stock to date and we currently intend to retain all of our future earnings, if any, to fund the development and growth of our business. As a result, capital appreciation, if any, of our common stock will be the sole source of gains for our common stockholders for the foreseeable future. Consequently, in the foreseeable future, our common stockholders will likely only experience a gain from their investment in our common stock if the price of our common stock increases.

If equity research analysts do not continue to publish research or reports about our business or if they issue unfavorable commentary or downgrade our common stock, the price of our common stock could decline.

The trading market for our common stock relies in part on the research and reports that equity research analysts publish about us and our business. We do not control these analysts. The price of our common stock could decline if one or more equity analysts downgrade our common stock or if analysts issue other unfavorable commentary or cease publishing reports about us or our business.

Anti-takeover provisions contained in our amended and restated certificate of incorporation and amended and restated bylaws, as well as provisions of Delaware law, could impair a takeover attempt.

Our amended and restated certificate of incorporation, amended and restated bylaws and Delaware law contain provisions which could have the effect of rendering more difficult, delaying or preventing an acquisition deemed undesirable by our board of directors. Our corporate governance documents include provisions:

- creating a classified board of directors whose members serve staggered three-year terms;
- authorizing "blank check" preferred stock, which could be issued by our board of directors without stockholder approval and may contain voting, liquidation, dividend, and other rights superior to our common stock;
- limiting the liability of, and providing indemnification to, our directors and officers;
- limiting the ability of our stockholders to call and bring business before special meetings;
- requiring advance notice of stockholder proposals for business to be conducted at meetings of our stockholders and for nominations of candidates for election to our board of directors;
- controlling the procedures for the conduct and scheduling of board of directors and stockholder meetings; and
- providing our board of directors with the express power to postpone previously scheduled annual meetings and to cancel previously scheduled special meetings.

These provisions, alone or together, could delay or prevent hostile takeovers and changes in control or changes in our management.

As a Delaware corporation, we are also subject to provisions of Delaware law, including Section 203 of the Delaware General Corporation law, which prevents some stockholders holding more than 15% of our outstanding common stock from engaging in certain business combinations without approval of the holders of substantially all of our outstanding common stock.

Any provision of our amended and restated certificate of incorporation, amended and restated bylaws or Delaware law that has the effect of delaying or deterring a change in control could limit the opportunity for our stockholders to receive a premium for their shares of our common stock, and could also affect the price that some investors are willing to pay for our common stock.

ITEM 1B. UNRESOLVED STAFF COMMENTS

Not applicable.

ITEM 2. PROPERTIES

We have leased approximately 17,705 square feet of office space at 1-3 Center Plaza, Boston, Massachusetts on February 12, 2019 for a term of one hundred and twenty-four months. We have also leased 5,952 square feet of office space at 175 Portland Street, 4th Floor, Boston, Massachusetts from May 15, 2014 to July 31, 2020. We have also leased an additional approximately 2,976 square feet of office space on the second floor of the same location from April 15, 2015 to July 31, 2020, with an option to extend the lease for three additional years. In addition, with the landlord's consent, we have subleased the 2,976 square feet of office space on the second floor to an unrelated third party beginning on January 1, 2017 and expiring on June 30, 2020. We have also leased 3,079 square feet of office space in San Diego, California, from October 1, 2015 to September 30, 2019. In January 2019, we extended the lease for office space in San Diego, California with a new term expiring on December 31, 2024. We believe that our existing facilities are adequate for our current needs. When our leases expire, we may renew the existing leases or look for additional or alternate space for our operations. We believe that any additional space we may require will be available on commercially reasonable terms.

ITEM 3. LEGAL PROCEEDINGS

As of the date of this Annual Report, we were not party to any legal matters or claims. In the future, we may become party to legal matters and claims arising in the ordinary course of business, the resolution of which we do not anticipate would have a material adverse impact on our financial position, results of operations or cash flows.

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 commenced trading under the symbol "ZFGN" on the NASDAQ Global Market on June 19, 2014. Prior to that time, there was no public market for our common stock. Our common stock in our initial public offering, or IPO, priced at $16.00 per share on June 18, 2014.

On March 1, 2019, the last reported sales price of our common stock on the NASDAQ Global Market was $4.62 and as of March 1, 2019, there were approximately 23 holders of record of our common stock. However, because many of our outstanding shares are held in accounts with brokers and other institutions, we believe we have more beneficial owners.

Dividend Policy

We have never declared or paid dividends on our common stock and do not expect to pay dividends on our common stock for the foreseeable future. Instead, we anticipate that all of our earnings in the foreseeable future will be used for the operation and growth of our business. Any future determination to declare dividends will be subject to the discretion of our board of directors and will depend on various factors, including applicable laws, our results of operations, financial condition, future prospects, and any other factors deemed relevant by our board of directors. In addition, the terms of our outstanding indebtedness restrict our ability to pay dividends, and any future indebtedness that we may incur could preclude us from paying dividends.

Equity Compensation Plan Information

For information regarding securities authorized for issuance under equity compensation plans, see Part III "Item 12—Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters."

Issuer Purchases of Equity Securities by the Issuer and Affiliated Purchasers

None.

ITEM 6. SELECTED FINANCIAL DATA

The selected financial data set forth below has been derived from our audited consolidated financial statements. The information set forth below should be read in conjunction with "Management's Discussion and Analysis of Financial Condition and Results of Operations" and the audited consolidated financial statements, and the notes thereto, and other financial information included herein. Our historical results are not necessarily indicative of our future results.

	Year Ended December 31,				
	2018	2017	2016	2015	2014
	(in thousands, except per share data)				
Statement of Operations Data:					
Revenue	$ —	$ —	$ —	$ —	$ —
Operating expenses:					
Research and development	47,929	40,839	39,936	54,618	27,391
General and administrative	13,193	12,160	18,289	19,195	8,141
Total operating expenses	61,122	52,999	58,225	73,813	35,532
Loss from operations	(61,122)	(52,999)	(58,225)	(73,813)	(35,532)
Other income (expense):					
Interest income	1,889	996	894	438	28
Interest expense	(1,898)	(165)	(529)	(806)	(870)
Foreign currency transaction (losses) gains, net	(237)	140	(18)	(105)	(104)
Total other (expense) income, net	(246)	971	347	(473)	(946)
Net loss	(61,368)	(52,028)	(57,878)	(74,286)	(36,478)
Accretion of redeemable convertible preferred stock to redemption value	—	—	—	—	(92)
Net loss attributable to common stockholders	$ (61,368)	$ (52,028)	$ (57,878)	$ (74,286)	$ (36,570)
Net loss per share attributable to common stockholders, basic and diluted (1)	$ (1.90)	$ (1.90)	$ (2.12)	$ (2.78)	$ (3.00)
Weighted average common shares outstanding, basic and diluted	32,229	27,433	27,298	26,756	12,189

	December 31,				
	2018	2017	2016	2015	2014
			(in thousands)		
Balance Sheet Data:					
Cash, cash equivalents and marketable securities	$ 118,066	$ 102,052	$ 129,194	$ 185,079	$ 115,462
Working capital (2)	108,024	97,632	121,005	171,567	110,297
Total assets	121,762	105,510	131,621	189,106	117,519
Notes payable, net of discount, long-term	15,185	20,000	—	3,453	6,177
Total stockholders' equity	93,271	78,217	121,727	169,110	104,441

(1) See Note 9 to our consolidated financial statements for further details on the calculation of basic and diluted net loss per share attributable to common stockholders.

(2) We define working capital as current assets less current liabilities.

ITEM 7. MANAGEMENT'S DISCUSSION AND ANALYSIS OF FINANCIAL CONDITION AND RESULTS OF OPERATIONS

The following discussion and analysis of our financial condition and results of operations should be read in conjunction with our "Selected Financial Data" and our consolidated financial statements, related notes and other financial information included elsewhere in this Annual Report on Form 10-K, or Annual Report. This discussion contains forward-looking statements that involve risks and uncertainties. Our actual results could differ materially from the results described, in or implied by, these forward-looking statements. Factors that could cause or contribute to those differences include, but are not limited to, those identified below and those discussed above in the section entitled "Risk Factors."

We caution readers not to place undue reliance on any forward-looking statements made by us, which speak only as of the date they are made. We disclaim any obligation, except as specifically required by law and the rules of the Securities and Exchange Commission, or SEC, to publicly update or revise any such statements to reflect any change in our expectations or in events, conditions or circumstances on which any such statements may be based, or that may affect the likelihood that actual results will differ from those set forth in the forward-looking statements.

Overview

We are a clinical-stage biopharmaceutical company leveraging our proprietary methionine aminopeptidase 2, or MetAP2, biology platform to develop novel therapies for patients affected by complex metabolic diseases. We have pioneered the study of MetAP2 inhibitors in both common and rare metabolic disorders and we are currently advancing programs for type 2 diabetes, Prader-Willi syndrome, or PWS, and liver diseases.

Our lead product candidate is ZGN-1061, a novel fumagillin-class MetAP2 inhibitor administered by subcutaneous injection, which is currently being profiled for its utility in the treatment of type 2 diabetes. Type 2 diabetes is a prevalent, chronic, progressive, multifactorial disease that leads to increased microvascular and macrovascular disease, and as such, increases risk of death from cardiovascular disease, stroke, and kidney failure. Type 2 diabetes is also a leading cause of lower-limb amputation and blindness. Existing treatments, while effective in reducing blood glucose levels, fail to reduce progression of the disease, which is driven by loss of function of insulin-producing beta cells and by loss of sensitivity to insulin action. It is estimated that approximately one-third of patients with type 2 diabetes progress to needing insulin (recently estimated to be a $20.0 billion market based on annual sales). New therapies are needed to improve glycemic control and reduce comorbidities of type 2 diabetes.

We have also initiated development of a second MetAP2 development candidate, ZGN-1258, which is administered by subcutaneous injection. We initiated investigational new drug application, or IND, enabling nonclinical activities in the first quarter of 2018, in preparation for filing an IND with the U.S. Food and Drug Administration, or FDA. In March 2019, we announced our decision to suspend plans to file an IND for ZGN-1258 in order to evaluate an unexpected finding in muscle tissue in four- and six-month long-term rodent toxicology studies. Nonclinical data showed degeneration and other anomalies in rat muscle tissue to different degrees in both vehicle and dose arms of the studies. The effects were absent from other animal species in long term models, and importantly, this observed finding is specific to ZGN-1258 and is not related to effects seen with any prior compound. We are taking the necessary steps to assess the unexpected effects we observed. We will continue to evaluate ZGN-1258, as well as explore other potential options within our portfolio of MetAP2 inhibitors, to address the devastating hyperphagia experienced by those with PWS. We continue to have a commitment to people with PWS and their families and we will continue to evaluate ZGN-1258 as well as explore other potential options within our portfolio of MetAP2 inhibitors.

PWS is a rare and complex genetic disorder characterized by physiologic, cognitive and behavioral symptoms including hyperphagia, uncontrollable hunger and its related behaviors, and obesity. Published population studies estimate that the prevalence of PWS in the United States and in the EU ranges from 1 in 8,000 to 1 in 50,000. The physiological drive to eat in patients with PWS is so powerful that they will go to great lengths to eat large quantities of food, even if it is spoiled, indigestible or unpalatable to others. Unsupervised patients will often eat to the point that it causes serious physical harm or death. As a result, caregivers are often forced to place locks and alarms on refrigerators and pantries that contain food. Despite attempts to control the access to food, the typical adult patient with PWS is morbidly obese and, based on evaluation of published survival data, has an average life expectancy of 32 years of age. Unfortunately, neither dietary intervention nor currently available pharmaceutical therapies bring meaningful benefits to patients with PWS and, as a result, they experience severe and life-threatening consequences of their condition. Furthermore, existing surgical techniques such as bariatric surgery are contraindicated in PWS, as patients with PWS often overeat to a point whereby they can rupture their stomachs, which is frequently a cause of death in this patient population.

We have launched a co-sponsored four-year natural history study to advance understanding of the medical history of and medical events in people with PWS. PATH for PWS, is our natural history study conducted in collaboration with the

Foundation for Prader-Willi Research, or FPWR, is independent of any specific development program and continues enrollment, with more than 400 of the 500-participant goal enrolled as of March 2019. The study is a non-interventional, observational study to evaluate occurrences of serious medical events in PWS, intended to inform development and clinical trial design for potential new treatments for PWS. The new ZGN-1258 findings do not impact the conduct of this study or our support of PATH for PWS.

Both ZGN-1061 and ZGN-1258 were discovered by our researchers as part of a multi-year campaign to identify highly potent and effective novel compounds with nonclinical safety profiles supportive of continued development. One core element of focus for optimization was to reduce or eliminate the potential for pro-thrombotic effects, a limiting factor that led to termination of development of our first-generation compound. To date, both new compounds have similar intrinsic potency against the MetAP2 enzyme and display appropriate activity in animal models of type 2 diabetes and obesity. We have observed degeneration and other anomalies in muscle tissue in rodent toxicology studies of ZGN-1258 as noted above. These effects were absent from other animal species in long term models and this finding has not been observed in any of our other MetAP2 inhibitors and appears to be specific to ZGN-1258.

We conducted a Phase 2 clinical trial for ZGN-1061 in Australia and New Zealand, which was designed to evaluate safety, tolerability, and glucose-lowering efficacy in patients with type 2 diabetes otherwise poorly controlled with non-insulin agents. The clinical trial met all of its primary objectives at the 1.8 mg dose, which included glycemic control, or change in A1C, and safety and tolerability. The 12-week data demonstrated that treatment with the 1.8 mg dose of ZGN-1061 produced substantially more improvement in A1C than a placebo dose. Progressive and notable reduction in body weight also occurred in patients treated with the highest dose tested (1.8 mg) versus placebo. The data showed a favorable tolerability profile for ZGN-1061, with no treatment-related serious adverse events and no cardiovascular, or CV, safety signals observed. Adverse events were primarily mild or moderate in severity, with no noted trends by dose or type of adverse event reported. We expect to report full results of the Phase 2 clinical trial at an upcoming medical meeting in 2019.

We received a letter from the FDA placing a full clinical hold on the IND for the first U.S. clinical trial of ZGN-1061, our second-generation, investigational MetAP2 inhibitor currently in development for the treatment of type 2 diabetes. The FDA cited the possibility of CV safety risk based on our prior compound and outlined multiple potential paths for moving forward, including nonclinical or clinical options, to address these concerns in the ongoing development of ZGN-1061. We are assessing these options and a possible path forward and plan to request a Type A meeting with the FDA. The ex-U.S. Phase 1 and Phase 2 clinical trials of ZGN-1061 have been completed with no CV safety signals.

In addition to the Phase 2 clinical data for ZGN-1061, nonclinical data on treatment with both ZGN-1061 and liraglutide suggest that combination therapy with these glucose-lowering agents may yield additive improvement in glycemic control and weight loss than either agent alone in patients with type 2 diabetes, demonstrating the potential effect of two complementary mechanisms – MetAP2 and glucose-dependent insulinotropic peptide, or GLP-1. From nonclinical data in a nonalcoholic steatohepatitis, or NASH, model, we further observed that ZGN-1061 markedly reduced liver weight, NAS score and markers of liver damage (ALT and AST). These NASH-related data, combined with previous gene expression data and clinical liver fat content data from Zafgen's first-generation MetAP2 inhibitor, suggest potential clinical value in treating liver-specific metabolic conditions. We anticipate that treatment with ZGN-1061 could improve multiple aspects of NASH, and we will evaluate the potential utility of ZGN-1061 as a NASH therapy in the setting of type 2 diabetes.

In 2017, we also initiated development of a third, highly optimized MetAP2 development candidate, ZGN-1345, which is administered via the oral route and is targeted to the liver. During the fourth quarter of 2018 we announced that ZGN-1345 has been formally advanced to development candidate stage as a differentiated third asset within our pipeline. Nonclinical models have shown positive preliminary results in multiple liver disease indications. Further nonclinical studies are ongoing.

Since our inception in November 2005, we have devoted substantially all of our resources to developing ZGN-1061, ZGN-1258, ZGN-1345, beloranib, ZGN-839 and additional MetAP2 inhibitors, building our intellectual property portfolio, developing manufacturing capabilities, business planning, raising capital, and providing general and administrative support for such operations. From our inception through our initial public offering, or IPO, in June 2014, we received gross proceeds of $104.0 million from sales of redeemable convertible preferred stock and, to a lesser extent, through the issuances of convertible promissory notes. In June 2014, we completed our IPO with net proceeds of $102.7 million after deducting underwriting discounts and commissions paid by us. In January 2015, we completed a follow-on offering of our common stock, with net proceeds of $130.0 million after deducting underwriting discounts and commissions paid by us. On July 2, 2018, we completed a public offering of our common stock, which resulted in the sale of 9,200,000 shares at a price of $7.50 per share, resulting in net proceeds of approximately $64.6 million after deducting underwriting discounts and commissions, as well as offering costs paid by us.

We have never generated any revenue and have incurred net losses in each year since our inception. We have an accumulated deficit of $350.9 million as of December 31, 2018. Our net loss was $61.4 million for the year ended

December 31, 2018 and $52.0 million for the year ended December 31, 2017. These losses have resulted principally from costs incurred in connection with in-licensing of technology, research and development activities and general and administrative costs associated with our operations. We expect to incur significant expenses and operating losses for the foreseeable future.

We expect to continue to incur expenses in connection with our ongoing activities, if and as we:

- advance the development of ZGN-1061 through Phase 2 clinical trials;
- advance the development of ZGN-1258 through further nonclinical studies and into clinical trials if warranted upon further evaluation of ZGN-1258;
- seek to identify and advance development of additional product candidates into clinical development and indications for our product candidates;
- seek to obtain regulatory approvals for our product candidates;
- add operational, financial and management information systems;
- add personnel, including personnel to support our product development and future commercialization; and
- maintain, leverage and expand our intellectual property portfolio.

As a result, we will need additional financing to support our continuing operations. Until such time that we can generate significant revenue from product sales, if ever, we expect to finance our operations through a combination of public equity, private equity, debt financings, or other sources, which may include collaborations with third parties. Arrangements with collaborators or others may require us to relinquish rights to certain of our technologies or product candidates. In addition, we may never successfully complete development of any of our product candidates, obtain adequate patent protection for our technology, obtain necessary regulatory approval for our product candidates or achieve commercial viability for any approved product candidates. Adequate additional financing may not be available to us on acceptable terms, or at all. Our failure to raise capital as and when needed would have a negative impact on our financial condition and our ability to pursue our business strategy. We will need to generate significant revenue to achieve profitability, and we may never do so.

We expect that our existing cash, cash equivalents and marketable securities as of December 31, 2018, will enable us to fund our operating expenses and capital expenditure requirements for a period of at least one year from the issuance date of this Annual Report. See "—Liquidity and Capital Resources."

Financial Operations Overview

Revenue

We have not generated any revenue from product sales since our inception, and do not expect to generate any revenue from the sale of products in the near future. If our development efforts result in clinical success and regulatory approval or collaboration agreements with third parties for our product candidates, we may generate revenue from those product candidates or collaborations.

Operating Expenses

The majority of our operating expenses since inception have consisted primarily of research and development activities, and general and administrative costs.

Research and Development Expenses. Research and development expenses, which consist primarily of costs associated with our product research and development efforts, are expensed as incurred. Research and development expenses consist primarily of:

- personnel costs, including salaries, related benefits and stock-based compensation for employees engaged in scientific research and development functions;
- third-party contract costs relating to research, formulation, manufacturing, nonclinical studies and clinical trial activities;
- external costs of outside consultants;

- payments made under our third-party licensing agreements;
- sponsored research agreements;
- laboratory consumables; and
- allocated facility-related costs.

We are currently primarily focused on developing ZGN-1061, ZGN-1258, ZGN-1345 and other early research activities and typically use our employee, consultant and infrastructure resources across our research and development programs. We track outsourced development costs by product candidate or development program, but we do not allocate personnel costs, external consultant costs, payments made under our licensing agreements or other internal costs to specific development programs or product candidates unless the payments are specifically identifiable to a development program or product candidate. We record our research and development expenses net of any research and development tax incentives we are entitled to receive from government authorities.

Research and development activities are central to our business. Product candidates in later stages of clinical development generally have higher development costs than those in earlier stages of clinical development, primarily due to the increased size and duration of later-stage clinical trials. We expect that our research and development expenses will increase in the foreseeable future as we pursue clinical development of our product candidates.

We cannot determine with certainty the duration and completion costs of the current or future clinical trials of our product candidates or if, when, or to what extent we will generate revenue from the commercialization and sale of any of our product candidates that obtain regulatory approval. We may never succeed in achieving regulatory approval for any of our product candidates. The duration, costs, and timing of clinical trials and development of our product candidates will depend on a variety of factors, including:

- the scope, rate of progress, and expense of clinical trials and other research and development activities;
- clinical trial results;
- uncertainties in clinical trial enrollment rate or design;
- significant and changing government regulation;
- the timing and receipt of any regulatory approvals; and
- the FDA's or other regulatory authority's influence on clinical trial design.

A change in the outcome of any of these variables with respect to the development of a product candidate could mean a significant change in the costs and timing associated with the development of that product candidate. For example, if the FDA, or another regulatory authority were to require us to conduct clinical trials beyond those that we currently anticipate will be required for the completion of clinical development of a product candidate, or if we experience significant delays in enrollment in any of our clinical trials, we could be required to expend significant additional financial resources and time on the completion of clinical development.

General and Administrative Expenses. General and administrative expenses consist primarily of personnel costs, consisting of salaries, related benefits and stock-based compensation, of our executive, finance, information technology, business and corporate development and other administrative functions. General and administrative expenses also include travel expenses, allocated facility-related costs not otherwise included in research and development expenses, insurance expenses, and professional fees for auditing, tax and legal services, including legal expenses to pursue patent protection of our intellectual property.

Other Income (Expense)

Interest income. Interest income consists of interest earned on our cash equivalents and marketable securities. Our interest income has not been significant due to low interest earned on invested balances. We anticipate that our interest income will decrease as we continue to incur operating losses.

Interest expense. Interest expense during the year ended December 31, 2018 relates to the loan and security agreement with Silicon Valley Bank, or the Term Loan, of $20.0 million, which closed on December 29, 2017. It bears a variable

interest at an annual rate of 1.25% above the prime rate, as well as a final payment equal to 8.0% of the Term Loan, which is being recorded as interest expense over the term through the maturity date using the effective-interest method.

Interest expense during the year ended December 31, 2017, relates to outstanding borrowings under a loan and security agreement with Oxford Finance LLC and Midcap Financial, or the 2014 Credit Facility, consisting of the stated interest of 8.1% per year due on outstanding borrowings, a final payment of 6% of amounts drawn down that was recorded as interest expense over the term through the maturity date using the effective-interest method, the amortization of deferred financing costs, the accretion of debt discounts relating to the 2014 Credit Facility.

Foreign currency transaction (losses) gains, net. Foreign currency transaction (losses) gains, net consists of the realized and unrealized gains and losses from foreign currency-denominated cash balances, vendor payables and tax-related receivables from the Australian government. We currently do not engage in hedging activities related to our foreign currency-denominated receivables and payables; as such, we cannot predict the impact of future foreign currency transaction gains and losses on our operating results. See "—Quantitative and Qualitative Disclosures about Market Risk."

Income Taxes

Since our inception in 2005, we have not recorded any U.S. federal or state income tax benefits for the net losses we have incurred in each year or our earned tax credits, due to our uncertainty of realizing a benefit from those items. As of December 31, 2018, we had net operating loss carryforwards that expire for federal and state income tax purposes of $55.7 million and $48.0 million, respectively, which begin to expire in 2026 and 2030, respectively. As of December 31, 2018, we had net operating loss carryforwards that were generated after December 31, 2017, of $9.5 million that do not expire. As of December 31, 2018, we also had available tax credit carryforwards for federal and state income tax purposes of $16.6 million and $3.4 million, respectively, which begin to expire in 2026 and 2022, respectively.

On December 22, 2017, the Tax Cuts and Jobs Act, or the TCJA, was signed into U.S. law. The TCJA includes a number of changes to existing tax law, including, among other things, a permanent reduction in the federal corporate income tax rate from a top marginal rate of 35% down to a flat rate of 21%, effective as of January 1, 2018, as well as limitation of the deduction for net operating losses to 80% of annual taxable income and elimination of net operating loss carrybacks, in each case, for losses arising in taxable years beginning after December 31, 2017 (though any such net operating losses may be carried forward indefinitely). The tax rate change resulted in a reduction in the gross amount of our deferred tax assets recorded as of December 31, 2017 with an offsetting reduction in the related valuation allowance, resulting in no income tax expense or benefit being recognized as of the enactment date of the TCJA.

JOBS Act

On April 5, 2012, the Jumpstart Our Business Startups Act, or the JOBS Act, was signed into law. The JOBS Act contains provisions that, among other things, reduce certain reporting requirements for an "emerging growth company." As an "emerging growth company," we are electing not to take advantage of the extended transition period afforded by the JOBS Act for the implementation of new or revised accounting standards and, as a result, we will comply with new or revised accounting standards on the relevant dates on which adoption of such standards is required for non-emerging growth companies. Section 107 of the JOBS Act provides that our decision not to take advantage of the extended transition period is irrevocable.

As an "emerging growth company" we are relying on other exemptions and reduced reporting requirements provided by the JOBS Act. As such, we have elected not to (i) provide an auditor's attestation report on our system of internal controls over financial reporting pursuant to Section 404, (ii) provide all of the compensation disclosure that may be required of non-emerging growth public companies under the Dodd-Frank Wall Street Reform and Consumer Protection Act, (iii) comply with any requirement that may be adopted by the Public Company Accounting Oversight Board regarding mandatory audit firm rotation or a supplement to the auditor's report providing additional information about the audit and the financial statements (auditor discussion and analysis), and (iv) disclose certain executive compensation-related items such as the correlation between executive compensation and performance and comparisons of the Chief Executive Officer's compensation to median employee compensation. These exemptions apply for a period of five years following the completion of our IPO in June 2014 or until we no longer meet the requirements of being an "emerging growth company," whichever is earlier. Barring any changes to the law, we will no longer be an emerging growth company in 2019.

Critical Accounting Policies and Significant Judgments and Estimates

Our consolidated financial statements are prepared in accordance with generally accepted accounting principles in the United States of America. The preparation of our consolidated financial statements and related disclosures requires us to

make estimates and assumptions that affect the reported amount of assets, liabilities, revenue, costs and expenses, and related disclosures. We believe that the estimates and assumptions involved in the accounting policies described below may have the greatest potential impact on our consolidated financial statements and, therefore, consider these to be our critical accounting policies. We evaluate our estimates and assumptions on an ongoing basis. Our actual results may differ from these estimates under different assumptions and conditions. See also Note 2 of our consolidated financial statements included elsewhere in this Annual Report for information about these critical accounting policies as well as a description of our other significant accounting policies.

Research and Development Expenses

As part of the process of preparing our consolidated financial statements, we are required to estimate our accrued research and development expenses. This process involves reviewing open contracts and purchase orders, communicating with our personnel and outside vendors to identify services that have been performed on our behalf and estimating the level of service performed and the associated costs incurred for the services when we have not yet been invoiced or otherwise notified of the actual costs. The majority of our service providers invoice us in arrears for services performed, on a pre-determined schedule or when contractual milestones are met; however, some require advance payments. We make estimates of our accrued expenses as of each balance sheet date in our consolidated financial statements based on facts and circumstances known to us at that time. Examples of estimated accrued research and development expenses include fees paid to:

- contract research organizations, or CROs, in connection with clinical trials;
- investigative sites or other providers in connection with clinical trials;
- vendors in connection with nonclinical development activities; and
- vendors related to product candidate manufacturing, development and distribution of clinical supplies.

We base our expenses related to clinical trials on our estimates of the services received and efforts expended pursuant to contracts with multiple CROs that conduct and manage clinical trials on our behalf. The financial terms of these agreements are subject to negotiation, vary from contract to contract and may result in uneven payment flows. There may be instances in which payments made to our vendors will exceed the level of services provided and result in a prepayment of the clinical expense, nonclinical expense, or manufacturing activities. Payments under some of these contracts depend on factors such as the successful enrollment of patients and the completion of clinical trial milestones. In accruing service fees, we estimate the time period over which services will be performed, enrollment of patients, number of sites activated and the level of effort to be expended in each period. If the actual timing of the performance of services or the level of effort varies from our estimate, we adjust the accrual or prepaid accordingly. Although we do not expect our estimates to be materially different from amounts actually incurred, our understanding of the status and timing of services performed relative to the actual status and timing of services performed may vary and may result in us reporting amounts that are too high or too low in any particular period. To date, we have not made any material adjustments to our prior estimates of accrued research and development expenses.

Stock-Based Compensation

We have historically issued equity awards to employees, directors and consultants, generally in the form of options to purchase shares of our common stock and, to a lesser extent, shares of restricted common stock. We measure stock-based awards granted to employees and directors at fair value on the date of grant and recognize the corresponding compensation expense of those awards over the requisite service period, which is generally the vesting period of the respective award. Generally, we issue stock options and restricted stock awards with only service-based vesting conditions and record the expense for these awards using the straight-line method. We measure stock-based awards granted to consultants and nonemployees at the fair value of the award on the date at which the related service is complete. Compensation expense is recognized over the period during which services are rendered by such consultants and nonemployees until completed. At the end of each financial reporting period prior to completion of the service, the fair value of these awards is re-measured using the then-current fair value of our common stock and updated assumption inputs in the Black-Scholes option-pricing model.

The fair value of each service-based stock option grant to employees and directors is estimated on the date of grant using the Black-Scholes option-pricing model. The Company estimates its expected volatility using a weighted average of the historical volatility of publicly-traded peer companies and its own common stock since its IPO in June 2014, and expects to continue to do so until such time as it has adequate historical data regarding the volatility of its own traded stock price for the duration of the expected term. The expected term of the Company's stock options has been determined utilizing the "simplified" method for awards that qualify as "plain-vanilla" options. The risk-free interest rate is determined by reference

to the U.S. Treasury yield curve in effect at the time of grant of the award for time periods approximately equal to the expected term of the award. Expected dividend yield is based on the fact that the Company has never paid cash dividends and does not expect to pay any cash dividends in the foreseeable future.

In October 2017, we granted market-based stock option awards which are valued using Monte Carlo simulation models. The number of options expected to vest, based on achievement of the specified market condition, is factored into the grant date Monte Carlo valuations. Compensation expense is recognized ratably over the attribution period.

The assumptions we used to determine the fair value of service-based stock options granted to employees and directors are as follows, presented on a weighted average basis:

	2018	2017	2016
Risk-free interest rate	2.77%	2.10%	1.40%
Expected term (in years)	6.17	6.17	6.18
Expected volatility	100%	93%	87%
Expected dividend yield	0%	0%	0%

The assumptions that we used to determine the fair value of the market-based stock options granted to employees in 2017 are as follows, presented on a weighted average basis:

	2017
Risk-free interest rate	2.24%
Expected term (in years)	6.30
Expected volatility	95%
Expected dividend yield	0%

These assumptions represented our best estimates, but the estimates involve inherent uncertainties and the application of our judgment. As a result, if factors change and we use significantly different assumptions or estimates, our stock-based compensation expense could be materially different. We recognize compensation expense for only the portion of awards that are expected to vest.

The following table summarizes the classification of our stock-based compensation expenses recognized in our consolidated statements of operations and comprehensive loss:

	Year Ended December 31,		
	2018	2017	2016
	(in thousands)		
Research and development	$ 5,476	$ 4,138	$ 3,543
General and administrative	4,151	4,163	6,390
	$ 9,627	$ 8,301	$ 9,933

As of December 31, 2018, we had unrecognized stock-based compensation expense related to our unvested service-based stock option awards of $10.8 million, which is expected to be recognized over the remaining weighted average vesting period of 2.2 years.

As of December 31, 2018, we had unrecognized stock-based compensation expense related to our unvested market-based stock option awards of $1.7 million, which is expected to be recognized over the remaining weighted average vesting period of 1.8 years.

Results of Operations

Comparison of Years Ended December 31, 2018 and 2017

The following table summarizes our results of operations for the years ended December 31, 2018 and 2017:

	Year Ended December 31,		
	2018	2017	Increase (Decrease)
	(in thousands)		
Statement of Operations Data:			
Revenue	$ —	$ —	$ —
Operating expenses:			
Research and development	47,929	40,839	7,090
General and administrative	13,193	12,160	1,033
Total operating expenses	61,122	52,999	8,123
Loss from operations	(61,122)	(52,999)	(8,123)
Other income (expense):			
Interest income	1,889	996	893
Interest expense	(1,898)	(165)	(1,733)
Foreign currency transaction (losses) gains, net	(237)	140	(377)
Total other (expense) income, net	(246)	971	(1,217)
Net loss	$ (61,368)	$ (52,028)	$ (9,340)

Research and development expenses

	Year Ended December 31,		
	2018	2017	Increase (Decrease)
	(in thousands)		
Direct research and development expenses by program:			
ZGN-1061:			
Nonclinical and manufacturing	$ 4,374	$ 11,945	$ (7,571)
Clinical trials	6,311	6,000	311
Subtotal	10,685	17,945	(7,260)
ZGN-1258	11,496	—	11,496
Discovery and screening	6,822	6,339	483
Beloranib	—	746	(746)
Subtotal	29,003	25,030	3,973
Unallocated expenses:			
Personnel related	8,955	7,851	1,104
Non-cash stock-based compensation	5,476	4,138	1,338
Consultants	2,231	2,286	(55)
Other	2,264	1,534	730
Subtotal	18,926	15,809	3,117
Total research and development expenses	$ 47,929	$ 40,839	$ 7,090

Research and development expenses for the year ended December 31, 2018 increased $7.1 million compared to the year ended December 31, 2017. The increase was primarily due to an increase of $11.5 million related to our ZGN-1258 program, as well as an increase in our unallocated expenses of $3.1 million and discovery and screening of $0.5 million, partially offset by decreased costs of $7.3 million associated with our ZGN-1061 program and $0.7 million associated with our beloranib program.

Costs associated with our ZGN-1258 program for the year ended December 31, 2018 are due to our advancement of the program in January 2018, and in the first quarter of 2018 our nonclinical efforts for evaluation of ZGN-1258 initially in the treatment of people affected by PWS. In March 2019, we announced our decision to suspend plans to file an IND for ZGN-

1258 in order to evaluate ZGN-1258 following an unexpected finding in muscle tissue in rodent toxicology studies. Based on our experience in MetAP2 inhibitor development, in 2018 we identified ZGN-1345, an orally dosed MetAP2 inhibitor specifically targeting the liver. Our discovery and screening costs have increased slightly by $0.5 million from the year ended December 31, 2018 as compared to the year ended December 31, 2017 due to the timing of expenses.

Unallocated expenses increased period over period primarily due to an increase of $1.3 million in non-cash stock-based compensation, as well as an increase in personnel related costs of $1.1 million. Non-cash stock-based compensation has increased primarily due to personnel transfers between functional areas and new employees. Personnel related expenses increased primarily due to the hiring of new employees and personnel transfers between functional areas.

Costs associated with our ZGN-1061 program decreased period over period by $7.3 million, primarily due to a decrease in nonclinical and manufacturing costs of $7.6 million. During the 2017 period, costs increased primarily as a result of additional nonclinical studies and drug product and drug substance activities, as we were planning for our Phase 2 clinical trial which commenced in the third quarter of 2017 in both Australia and New Zealand, for which we enrolled 137 patients in a 12-week clinical trial. Partially offsetting the decrease in nonclinical and manufacturing costs of our ZGN-1061 program was an increase in costs associated with our clinical trials for our ZGN-1061 program of $0.3 million. The expenses during the 2017 period were for final costs for a Phase 1 clinical trial of ZGN-1061 in the Netherlands, which was comprised of 39 patients in a single ascending dose, or SAD, portion and 29 patients in a multiple ascending dose, or MAD, portion, while the expenses during the 2018 period are for the larger Phase 2 clinical trial.

General and administrative expenses

	Year Ended December 31,		
	2018	2017	Increase (Decrease)
	(in thousands)		
Personnel related	$ 2,971	$ 2,320	$ 651
Non-cash stock-based compensation	4,151	4,163	(12)
Professional fees	3,960	3,908	52
Other	2,111	1,769	342
Total general and administrative expenses	$ 13,193	$ 12,160	$ 1,033

General and administrative expenses for the year ended December 31, 2018 increased $1.0 million compared to the year ended December 31, 2017. The increase was due to an increase in personnel related costs of $0.7 million, professional fees of less than $0.1 million and other costs of $0.3 million. Personnel related costs increased as a result of hiring new employees. Professional fees increased primarily due to recruiting expenses for new key employees and legal expenses associated with the filing of multi-country patents. Other general and administrative expenses increased primarily due to fees associated with our SEC filings and software costs. These increases were offset by a decrease in non-cash stock-based compensation of less than $0.1 million. Non-cash stock-based compensation expense decreased due mainly to personnel transfers between functional areas.

Other income (expense), net

Interest expense. Interest expense for the year ended December 31, 2018 and 2017 was $1.9 million and $0.2 million, respectively. Interest expense during the year ended December 31, 2018 relates to the Term Loan of $20.0 million, which closed on December 29, 2017. It bears a variable interest at an annual rate of 1.25% above the prime rate, as well as a final payment equal to 8.0% of the Term Loan, which is being recorded as interest expense over the term through the maturity date using the effective-interest method.

Interest expense during the year ended December 31, 2017 was related to interest expense on our outstanding borrowings under the 2014 Credit Facility, which was fully repaid in December 2017. Interest expense consists primarily of the stated interest of 8.1% per year due on outstanding borrowings. It also includes expense related to the final payment of 6% of amounts drawn down that was recorded over the term through the maturity date using the effective-interest method and the amortization of deferred financing costs and debt discounts relating to the 2014 Credit Facility.

Interest income. Interest income of $1.9 million and $1.0 million for the years ended December 31, 2018 and 2017, respectively, was related to interest earned on our marketable securities balances.

Foreign currency transaction (losses) gains, net. We had foreign currency transaction losses of $(0.2) million and gains of $0.1 million for the years ended December 31, 2018 and 2017, respectively. Foreign currency transaction gains and losses consisted of the realized and unrealized gains and losses from foreign currency-denominated cash balances, vendor payables and tax-related receivables from the Australian government, generally reflecting the fluctuation of the Australian dollar relative to the U.S. dollar.

Comparison of Years Ended December 31, 2017 and 2016

The following table summarizes our results of operations for the years ended December 31, 2017 and 2016:

	Year Ended December 31,		
	2017	2016	Increase (Decrease)
	(in thousands)		
Statement of Operations Data:			
Revenue	$ —	$ —	$ —
Operating expenses:			
Research and development	40,839	39,936	903
General and administrative	12,160	18,289	(6,129)
Total operating expenses	52,999	58,225	(5,226)
Loss from operations	(52,999)	(58,225)	5,226
Other income (expense):			
Interest income	996	894	102
Interest expense	(165)	(529)	364
Foreign currency transaction gains (losses), net	140	(18)	158
Total other income (expense), net	971	347	624
Net loss	$ (52,028)	$ (57,878)	$ 5,850

Research and development expenses

	Year Ended December 31,		
	2017	2016	Increase (Decrease)
	(in thousands)		
Direct research and development expenses by program:			
ZGN-1061			
Nonclinical and manufacturing	$ 11,945	$ 5,539	$ 6,406
Clinical trials	6,000	2,054	3,946
Subtotal	17,945	7,593	10,352
Discovery and screening	6,339	393	5,946
Beloranib	746	13,635	(12,889)
ZGN-839	—	858	(858)
Subtotal	25,030	22,479	2,551
Unallocated expenses:			
Personnel related	7,851	8,694	(843)
Non-cash stock-based compensation	4,138	3,543	595
Consultants	2,286	3,256	(970)
Other	1,534	1,964	(430)
Subtotal	15,809	17,457	(1,648)
Total research and development expenses	$ 40,839	$ 39,936	$ 903

Research and development expenses for the year ended December 31, 2017 increased $0.9 million compared to the year ended December 31, 2016. The increase was primarily due to an increase of $10.4 million related to our ZGN-1061 program, as well as an increase in discovery and screening expenses of $5.9 million, partially offset by decreased costs of $12.9 million in our beloranib program and a decrease of $1.6 million associated with our unallocated expenses.

Costs associated with our ZGN-1061 program increased period over period by $10.4 million. In the third quarter of 2016 we initiated a Phase 1 clinical trial for ZGN-1061 which completed recruiting and dosing patients in the first quarter of 2017. The overall increase is primarily due to additional nonclinical studies as well as drug product and drug substance activities as we commenced our Phase 2 clinical trial in the third quarter of 2017 in both Australia and New Zealand, for which we enrolled 137 patients in a 12-week clinical trial. The expenses during the 2016 period were for startup costs for a Phase 1 clinical trial of ZGN-1061 in the Netherlands, which was comprised of 39 patients in a SAD portion and 29 patients in a MAD portion.

Of the decrease in costs associated with our beloranib program, clinical trials costs decreased by $8.3 million period over period and nonclinical and manufacturing costs decreased $4.6 million period over period, both as a result of the suspension of our beloranib program in July 2016. During the year ended December 31, 2016, we reported topline clinical data from our Phase 2b clinical trial in patients with severe obesity complicated by type 2 diabetes and our U.S. Phase 3 clinical trial in patients with PWS. Prior to the FDA placing the IND application for beloranib on full clinical hold in December 2015, we suspended dosing of patients in the randomized portion of both of these trials in October 2015. In July 2016, we announced the suspension of our beloranib program.

Unallocated expenses decreased period over period primarily due to a decrease of $1.0 million in consultants, as well as a decrease in personnel related costs of $0.8 million. Consultant costs decreased primarily related to our beloranib program which we suspended in July 2016. Personnel related expenses decreased primarily from a reduction in the number of employees for the 2017 period as compared to the 2016 period, as we had a reduction in workforce which took place in July 2016.

General and administrative expenses

	Year Ended December 31,		
	2017	2016	Increase (Decrease)
	(in thousands)		
Personnel related	$ 2,320	$ 4,401	$ (2,081)
Non-cash stock-based compensation	4,163	6,390	(2,227)
Professional fees	3,908	5,489	(1,581)
Other	1,769	2,009	(240)
Total general and administrative expenses	$ 12,160	$ 18,289	$ (6,129)

General and administrative expenses for the year ended December 31, 2017 decreased $6.1 million compared to the year ended December 31, 2016. The decrease was due to decreases in non-cash stock-based compensation expense of $2.2 million, personnel related costs of $2.1 million and professional fees of $1.6 million. Non-cash stock-based compensation expense decreased due mainly to forfeited stock options related to the reduction in workforce in July 2016, as well as a lower stock option grant price for the 2017 annual grant. Personnel related expenses decreased primarily from a reduction in the number of employees for the 2017 period as compared to the 2016 period, from the reduction in workforce which took place in July 2016. Professional fees decreased primarily due to lower legal fees as the plaintiffs for the class action lawsuit had filed a notice of appeal to the First Circuit Court of Appeals and on April 7, 2017, the dismissal with prejudice was affirmed. The decrease was also due to lower commercial readiness costs and investor relations and public relations costs in the 2017 period as compared to the same period in 2016, primarily as a result of suspending development of beloranib in July 2016.

Other income (expense), net

Interest expense. Interest expense for the year ended December 31, 2017 and 2016 of $0.2 million and $0.5 million, respectively, was related to interest expense on our outstanding borrowings under the 2014 Credit Facility, which was fully repaid in December 2017. Interest expense consists primarily of the stated interest of 8.1% per year due on outstanding borrowings. It also includes expense related to the final payment of 6% of amounts drawn down that was recorded over the term through the maturity date using the effective-interest method and the amortization of deferred financing costs and debt discounts relating to the 2014 Credit Facility.

Interest income. Interest income of $1.0 million and $0.9 million for the years ended December 31, 2017 and 2016, respectively, was related to interest earned on our marketable securities balances.

Foreign currency transaction gains (losses), net. We had foreign currency transaction gains of $0.1 million for the year ended December 31, 2017 and no impact in 2016. Foreign currency transaction gains and losses consisted of the realized and unrealized gains and losses from foreign currency-denominated cash balances, vendor payables and tax-related receivables from the Australian government, generally reflecting the fluctuation of the Australian dollar relative to the U.S. dollar.

Liquidity and Capital Resources

As of December 31, 2018, we had cash, cash equivalents and marketable securities totaling $118.1 million. We invest our cash in money market funds, commercial paper, certificates of deposits, U.S. government securities and corporate bonds, with the primary objectives to preserve principal, provide liquidity and maximize income without significantly increasing risk.

Since our inception in November 2005, we have not generated any revenue and have incurred recurring net losses. As of December 31, 2018, we had an accumulated deficit of $350.9 million. Prior to our IPO in June 2014, we funded our operations primarily through sales of redeemable convertible preferred stock and, to a lesser extent, through the issuances of convertible promissory notes and a loan security agreement. From our inception through our IPO in June 2014, we received gross proceeds of $104.0 million from such transactions. In June 2014, we completed our IPO with net proceeds of $102.7 million after deducting underwriting discounts and commissions paid by us. We also incurred offering costs of $2.5 million related to the IPO. In January 2015, we completed a follow-on offering of our common stock, which resulted in the sale of 3,942,200 shares at a price of $35.00 per share. We received net proceeds from the follow-on offering of $130.0 million based upon the price of $35.00 per share and after deducting underwriting discounts and commissions paid by us. We also incurred offering costs of $0.5 million related to the follow-on offering. On July 2, 2018, we completed a public offering of our common stock, which resulted in the sale of 9,200,000 shares at a price of $7.50 per share, resulting in net proceeds of approximately $64.6 million after deducting underwriting discounts and commissions, as well as offering costs paid by us.

On November 9, 2018, we entered into a sales agreement, or the Sales Agreement, with Cowen and Company, LLC, or Cowen, to sell shares of our common stock, with aggregate gross sales proceeds of up to $50.0 million, from time to time, through an at-the-market equity offering program under which Cowen will act as its sales agent. Through December 31, 2018 we have not sold any shares under the Sales Agreement.

On December 29, 2017, we entered into a loan and security agreement with Silicon Valley Bank, or the Term Loan. The Term Loan provided for borrowings of $20.0 million. On December 29, 2017, we received proceeds of $20.0 million from the issuance of a promissory note. The promissory note issued under the Term Loan is collateralized by substantially all of our personal property, other than our intellectual property.

Upon entering into this Term Loan, we are obligated to make monthly, interest-only payments until March 29, 2019 and, thereafter, to pay 33 consecutive, equal monthly installments of principal and interest from April 1, 2019 through December 1, 2021. The outstanding Term Loan bears a variable interest at an annual rate of 1.25% above the prime rate, which was 5.5% at December 31, 2018. In addition, a final payment equal to 8.0% of the Term Loan is due upon the earlier of the maturity date, acceleration of the Term Loan or prepayment of all or part of the Term Loan. We accrue the final payment amount of $1.6 million, to outstanding debt by charges to interest expense using the effective-interest method from the date of issuance through the maturity date.

Additionally, we, as the borrower, are required to maintain a minimum cash, cash equivalents and marketable securities balance at Silicon Valley Bank of no less than 105% of the total outstanding principal balance of the Term Loan, which as of December 31, 2018 and December 31, 2017 was $21.0 million.

Further, as of 45 days after the Term Loan was entered in, we must maintain a balance of unrestricted cash, cash equivalents and marketable securities at Silicon Valley Bank in an amount not less than the greater of (i) $55.0 million and (ii) sixty-five percent (65%) of all of our cash, cash equivalents and marketable securities. If we do not meet this requirement it will not be considered an event of default provided we immediately secure 87.5% of the principal balance in a restricted cash account.

There are negative covenants restricting our activities, including limitations on dispositions, mergers or acquisitions; encumbering or granting a security interest in our intellectual property; incurring indebtedness or liens; paying dividends; making certain investments; permit the aggregate value of cash maintained by our Australian subsidiary not to exceed $4.0 million and certain other business transactions.

The Term Loan also includes events of default, the occurrence and continuation of any of which provides the lenders the right to exercise remedies against us and the collateral securing the loans under the Term Loan, including cash in the

amount of the outstanding balance. These events of default include, among other things, failure to pay any amounts due under the Term Loan, insolvency, the occurrence of a material adverse event, the occurrence of any default under certain other indebtedness and a final judgment against us in an amount greater than $0.3 million.

The following table summarizes our sources and uses of cash for each of the periods presented below:

	Year Ended December 31,		
	2018	2017	2016
	(in thousands)		
Net cash used in operating activities	$ (51,487)	$ (43,784)	$ (51,975)
Net cash (used in) provided by investing activities	(6,867)	35,647	51,447
Net cash provided by (used in) financing activities	66,908	16,562	(2,715)
Net increase (decrease) in cash and cash equivalents	$ 8,554	$ 8,425	$ (3,243)

Net cash used in operating activities

During the year ended December 31, 2018, operating activities used $51.5 million of cash, resulting from our net loss of $61.4 million, partially offset by non-cash charges of $9.9 million. Our net loss was primarily attributed to research and development activities related to our ZGN-1061 program, our ZGN-1258 program, discovery and screening and our general and administrative expenses. Our net non-cash charges during the year ended December 31, 2018, consisted primarily of stock-based compensation expense of $9.6 million. Net cash used in changes in our operating assets and liabilities during the year ended December 31, 2018, consisted primarily of a $1.1 million increase in accounts payable and accrued expenses, $0.2 million decrease in prepaid expenses and other current assets, partially offset by a $0.7 million increase in tax incentive receivable.

During the year ended December 31, 2017, operating activities used $43.8 million of cash, resulting from our net loss of $52.0 million, partially offset by non-cash charges of $8.3 million. Our net loss was primarily attributed to research and development activities related to our ZGN-1061 program, discovery and screening and our general and administrative expenses, as we had no revenue in the period. Our net non-cash charges during the year ended December 31, 2017, consisted primarily of stock-based compensation expense of $8.3 million. Net cash used in changes in our operating assets and liabilities during the year ended December 31, 2017, consisted primarily of a $1.0 million increase in accounts payable and accrued expenses, partially offset by a $0.6 million increase in prepaid expenses and other current assets and a $0.6 million increase in tax incentive receivable.

During the year ended December 31, 2016, operating activities used $52.0 million of cash, resulting from our net loss of $57.9 million and changes in our operating assets and liabilities of $5.5 million, partially offset by non-cash charges of $11.4 million. Our net loss was primarily attributed to research and development activities related to our beloranib program, our ZGN-1061 program, and our general and administrative expenses, as we had no revenue in the period. Our net non-cash charges during the year ended December 31, 2016, consisted primarily of stock-based compensation expense of $10.1 million. Net cash used in changes in our operating assets and liabilities during the year ended December 31, 2016, consisted primarily of a $6.9 million decrease in accounts payable and accrued expenses, partially offset by a $0.4 million decrease in prepaid expenses and other current assets and a $1.0 million decrease in tax incentive receivable.

Net cash (used in) provided by investing activities

During the year ended December 31, 2018, investing activities used $6.9 million of cash resulting from purchases of marketable securities of $117.1 million and purchases of equipment of $0.1 million. These uses were partially offset by proceeds from maturities of marketable securities of $110.4 million.

During the year ended December 31, 2017, investing activities provided $35.6 million of cash resulting from proceeds from sales and maturities of marketable securities of $150.2 million, offset by the use of cash for purchases of marketable securities of $114.5 million and purchases of property and equipment of $0.1 million.

During the year ended December 31, 2016, investing activities provided $51.4 million of cash resulting from proceeds from sales and maturities of marketable securities of $188.6 million, offset by the use of cash for purchases of marketable securities of $136.5 million and purchases of property and equipment of $0.7 million.

Net cash provided by (used in) financing activities

During the year December 31, 2018, net cash provided by financing activities of $66.9 million was the result of net proceeds of $64.6 million from our July 2, 2018 public offering of common stock and $2.4 million relating to the exercise of common stock options and common stock purchased under our 2014 Employee Stock Purchase Plan.

During the year ended December 31, 2017, net cash provided by financing activities of $16.6 million was the result of proceeds of $20.0 million from our notes payable, as well as $0.2 million received from proceeds relating to the exercise of common stock options and common stock purchased under our 2014 Employee Stock Purchase Plan, partially offset by payments of $3.6 million related to our notes payable.

During the year ended December 31, 2016, financing activities used $2.9 million for payments related to our notes payable, partially offset by $0.2 million received from proceeds relating to the exercise of common stock options and common stock purchased under our 2014 Employee Stock Purchase Plan.

Operating Capital Requirements

ZGN-1061 is currently in Phase 2 clinical development and ZGN-1258 and ZGN-1345 are in nonclinical development, therefore we expect to continue to incur significant expenses and operating losses for the foreseeable future. We anticipate that we will continue to incur expenses, if and as we seek to:

- resolve the FDA-imposed full clinical hold on ZGN-1061;
- advance the development of ZGN-1061 through Phase 2 clinical trials;
- advance the development of ZGN-1258 (if further evaluation warrants development) and ZGN-1345 through nonclinical and clinical development and if successful, later-stage clinical trials;
- seek to identify additional product candidates and indications for our product candidates;
- seek to obtain regulatory approvals for our product candidates;
- add operational, financial and management information systems;
- add personnel, including personnel to support our product development and future commercialization; and
- maintain, leverage and expand our intellectual property portfolio.

We expect that our existing cash and cash equivalents and marketable securities as of December 31, 2018, will enable us to fund our operating expenses and capital expenditure requirements for a period of at least one year from the issuance date of this Annual Report. We have based this estimate on assumptions that may prove to be wrong, and we may use our available capital resources sooner than we currently expect. Because of the numerous risks and uncertainties associated with the development ZGN-1061, ZGN-1258 and ZGN-1345 and because the extent to which we may enter into collaborations with third parties for the development of these product candidates is unknown, we are unable to estimate the amounts of increased capital outlays and operating expenses associated with completing the research and development of our product candidates. Our future capital requirements for ZGN-1061, ZGN-1258 and ZGN-1345 will depend on many factors, including:

- the costs, timing and outcome of regulatory review;
- the costs of future research and development activities, including clinical trials;
- the costs of preparing, filing and prosecuting patent applications, maintaining and enforcing our intellectual property rights and defending intellectual property-related claims;
- the extent to which we acquire or in-license other products, product candidates, or technologies; and
- our ability to establish any future collaboration arrangements on favorable terms, if at all.

Until such time, if ever, as we can generate substantial product revenue, we expect to finance our cash needs through a combination of equity offerings, debt financings, collaborations, strategic alliances and licensing arrangements. To the extent that we raise additional capital through the sale of equity or convertible debt securities, the ownership interest of our stockholders will be diluted, and the terms of these securities may include liquidation or other preferences that adversely affect the rights of our common stockholders. Debt financing, if available, may involve agreements that include covenants limiting or restricting our ability to take specific actions, such as incurring additional debt, making capital expenditures or

declaring dividends and may require the issuance of warrants, which could potentially dilute their ownership interest. If we raise additional funds through collaborations, strategic alliances or licensing arrangements with third parties, we may have to relinquish valuable rights to our technologies, future revenue streams, research programs or grant licenses on terms that may not be favorable to us. If we are unable to raise additional funds through equity or debt financings when needed, we may be required to delay, limit, reduce or terminate our product development or future commercialization efforts or grant rights to develop and market our product candidates that we would otherwise prefer to develop and market ourselves.

Since our inception in 2005, we have not recorded any U.S. federal or state income tax benefits for the net losses we have incurred in each year or our earned tax credits, due to our uncertainty of realizing a benefit from those items. As of December 31, 2018, we had net operating loss carryforwards that expire for federal and state income tax purposes of $55.7 million and $48.0 million, respectively, which begin to expire in 2026 and 2030, respectively. As of December 31, 2018, we had net operating loss carryforwards that were generated after December 31, 2017, of $9.5 million that do not expire. As of December 31, 2018, we also had available tax credit carryforwards for federal and state income tax purposes of $16.6 million and $3.4 million, respectively, which begin to expire in 2026 and 2022, respectively. We have not completed a study to assess whether an ownership change, generally defined as a greater than 50% change (by value) in the equity ownership of our corporate entity over a three-year period, has occurred or whether there have been multiple ownership changes since our inception, due to the significant costs and complexities associated with such studies. Accordingly, our ability to utilize our tax carryforwards may be limited. Additionally, U.S. tax laws limit the time during which these carryforwards may be utilized against future taxes. As a result, we may not be able to take full advantage of these carryforwards for federal and state tax purposes.

Contractual Obligations and Commitments

The following table summarizes our contractual obligations as of December 31, 2018 and the effect such obligations are expected to have on our liquidity and cash flow in future periods:

	Payments Due by Period				
	Total (2) (3)	Less Than 1 Year	1-3 Years	3-5 Years	More Than 5 Years
	(in thousands)				
Operating lease commitments (1)	$ 690	$ 464	$ 226	$ —	$ —
Debt commitments (4)	21,600	5,455	16,145	—	—
	$ 22,290	$ 5,919	$ 16,371	$ —	$ —

(1) We entered into an operating lease for office space in Boston, Massachusetts on May 15, 2014, effective as of July 28, 2014, with a term expiring on July 31, 2017, and an option to extend the lease for three additional years. In March 2015, we entered into an operating lease for additional office space in Boston, Massachusetts, effective as of April 15, 2015, with a term expiring on July 31, 2017, and two options to extend the lease for three additional years each. In October 2015, we entered into an operating lease for office space in San Diego, California, effective as of October 1, 2015, with a term expiring on September 30, 2019, and an option to extend the lease for five additional years. In January 2017, we extended the leases for both office spaces in Boston, Massachusetts, with new terms expiring on July 31, 2020. In addition, we have subleased 2,976 square feet of office space in Boston, Massachusetts to an unrelated third party beginning on January 1, 2017 and expiring on June 30, 2020 and we expect to receive approximately $0.2 million in sublease rental income from January 1, 2019 through the end of the sublease term.

(2) We have acquired exclusive rights to develop patented compounds and related know-how under licensing agreements for beloranib with two third parties. The licensing rights obligate us to make payments to the licensors for license fees, milestones, license maintenance fees and royalties. We are also responsible for patent prosecution costs. We are obligated to make future milestone payments under these agreements of up to $12.3 million, upon achieving certain pre-commercialization milestones, such as clinical trials and government approvals, and up to $12.5 million upon achieving certain product commercialization milestones. In addition, under one of the license agreements, we are obligated to pay up to $1.3 million with respect to each subsequent licensed product, if any, that is a new chemical entity. In addition, we will owe single-digit royalties on sales of commercial products developed using these licensed technologies, if any. We are obligated to pay to the licensors a percentage of fees received if and when we sublicense the technologies. As of December 31, 2018, we had not yet developed a commercial product using the licensed technologies and we had not entered into any sublicense agreements for the technologies.

(3) We enter into contracts in the normal course of business with clinical research organizations for clinical trials, nonclinical research studies and testing, manufacturing and other services and products for operating purposes. These

contracts generally provide for termination upon notice, and therefore we believe that our non-cancelable obligations under these agreements are not material.

(4) Debt commitments include principal, interest, and an 8% final payment of the amounts drawn under the Term Loan.

Off-Balance Sheet Arrangements

During the periods presented we did not have and we do not currently have, any off-balance sheet arrangements, as defined under Securities and Exchange Commission rules, such as relationships with unconsolidated entities or financial partnerships, which are often referred to as structured finance or special purpose entities, established for the purpose of facilitating financing transactions that are not required to be reflected on our balance sheets.

Recently Issued Accounting Pronouncements

Please read Note 2 to our consolidated financial statements included in Part II, Item 8, "Financial Statements and Supplementary Data," of this Annual Report for a description of recent accounting pronouncements applicable to our business.

ITEM 7A. QUANTITATIVE AND QUALITATIVE DISCLOSURE ABOUT MARKET RISK

Interest Rate Fluctuation Risk

Our cash, cash equivalents, and marketable securities as of December 31, 2018 consisted of cash, corporate bonds, commercial paper, certificates of deposits and money market accounts. The primary objectives of our investment activities are to preserve principal, provide liquidity and maximize income without significantly increasing risk. Our primary exposure to market risk is interest income sensitivity, which is affected by changes in the general level of U.S. interest rates. If market interest rates were to increase immediately and uniformly by 50 basis points, or one-half of a percentage point, from levels as of December 31, 2018, the net fair value of our interest-sensitive financial instruments would result in a hypothetical decline of $0.1 million.

Foreign Currency Exchange Risk

Foreign currency transaction exposure results primarily from transactions with our contract research organizations, or CROs, and other providers related to our clinical trials that are denominated in currencies other than the functional currency of the legal entity in which the transaction is recorded by us, primarily the Australian dollar. Any transaction gains or losses resulting from currency fluctuations is recorded on a separate line in our consolidated statement of operations. Net foreign currency transaction (losses) gains of $(0.2) million, $0.1 million and less than $(0.1) million were recorded for the years ended December 31, 2018, 2017 and 2016, respectively.

Currently, our largest foreign currency exposures are those with respect to the Australian dollar. Relative to foreign currency exposures existing as of December 31, 2018, a 10% unfavorable movement in foreign currency exchange rates would expose us to an increased net loss. For the year ended December 31, 2018, we estimated that a 10% unfavorable movement in foreign currency exchange rates would have increased our net loss by $0.2 million. This amount is based on a sensitivity analysis performed on our financial position as of December 31, 2018. We have experienced and will continue to experience fluctuations in our net loss as a result of revaluing our assets and liabilities that are not denominated in the functional currency of the entity that recorded the asset or liability. At this time, we do not hedge our foreign currency risk.

ITEM 8. FINANCIAL STATEMENTS AND SUPPLEMENTAL DATA

INDEX TO CONSOLIDATED FINANCIAL STATEMENTS

Report of Independent Registered Public Accounting Firm

To the Board of Directors and Shareholders of
Zafgen, Inc.

Opinion on the Financial Statements

We have audited the accompanying consolidated balance sheets of Zafgen Inc., and its subsidiaries as of December 31, 2018 and 2017, and the related consolidated statements of operations and comprehensive loss, of changes in stockholders' equity and of cash flows for each of the three years in the period ended December 31, 2018, including the related notes (collectively referred to as 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, 2018 and 2017, and the results of their operations and their cash flows for each of the three years in the period ended December 31, 2018 in conformity with accounting principles generally accepted in the United States of America.

Basis for Opinion

These consolidated financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on the Company's 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 of these consolidated financial statements 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.

Emphasis of matter

As discussed in Note 1 to the consolidated financial statements, the Company will require additional financing to fund future operations and debt payments. Management's plans in regard to this matter are described in Note 1.

/s/ PricewaterhouseCoopers LLP
Boston, Massachusetts
March 14, 2019

We have served as the Company's auditor since 2013.

PART I—FINANCIAL INFORMATION

Item 1. Financial Statements

ZAFGEN, INC.

CONSOLIDATED BALANCE SHEETS
(In thousands, except share and per share data)

	December 31,	
	2018	**2017**
Assets		
Current assets:		
Cash and cash equivalents	$ 49,331	$ 40,777
Marketable securities	68,735	61,275
Tax incentive receivable	1,536	946
Prepaid expenses and other current assets	1,728	1,927
Total current assets	121,330	104,925
Property and equipment, net	375	528
Other assets	57	57
Total assets	$ 121,762	$ 105,510
Liabilities and Stockholders' Equity		
Current liabilities:		
Accounts payable	$ 3,590	$ 3,020
Accrued expenses	4,261	4,273
Notes payable, current	5,455	—
Total current liabilities	13,306	7,293
Notes payable, long-term	15,185	20,000
Total liabilities	28,491	27,293
Commitments and contingencies (Note 10)		
Stockholders' equity:		
Preferred stock; $0.001 par value per share; 5,000,000 shares authorized as of December 31, 2018 and 2017; no shares issued and outstanding as of and December 31, 2018 and 2017	—	—
Common stock, $0.001 par value per share; 115,000,000 shares authorized as of December 31, 2018 and 2017; 37,287,221 and 27,489,457 shares issued and outstanding as of December 31, 2018 and 2017, respectively	37	27
Additional paid-in capital	444,212	367,825
Accumulated deficit	(350,945)	(289,577)
Accumulated other comprehensive loss	(33)	(58)
Total stockholders' equity	93,271	78,217
Total liabilities and stockholders' equity	$ 121,762	$ 105,510

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

ZAFGEN, INC.

CONSOLIDATED STATEMENTS OF OPERATIONS AND COMPREHENSIVE LOSS
(In thousands, except share and per share data)

	Year Ended December 31,		
	2018	**2017**	**2016**
Revenue	$ —	$ —	$ —
Operating expenses:			
Research and development	47,929	40,839	39,936
General and administrative	13,193	12,160	18,289
Total operating expenses	61,122	52,999	58,225
Loss from operations	(61,122)	(52,999)	(58,225)
Other income (expense):			
Interest income	1,889	996	894
Interest expense	(1,898)	(165)	(529)
Foreign currency transaction (losses) gains, net	(237)	140	(18)
Total other (expense) income, net	(246)	971	347
Net loss	$ (61,368)	$ (52,028)	$ (57,878)
Net loss per share, basic and diluted	$ (1.90)	$ (1.90)	$ (2.12)
Weighted average common shares outstanding, basic and diluted	32,228,721	27,433,239	27,297,934
Comprehensive loss:			
Net loss	$ (61,368)	$ (52,028)	$ (57,878)
Other comprehensive loss:			
Unrealized gain on marketable securities	25	22	127
Total other comprehensive gain	25	22	127
Total comprehensive loss	$ (61,343)	$ (52,006)	$ (57,751)

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

ZAFGEN, INC.

CONSOLIDATED STATEMENTS OF CHANGES IN STOCKHOLDERS' EQUITY
(In thousands, except share data)

	Common Stock		Additional Paid-in	Accumulated	Accumulated Other Comprehensive	Total Stockholders'
	Shares	Par Value	Capital	Deficit	Loss	Equity
Balances at December 31, 2015	27,242,503	$ 27	$ 348,961	$ (179,671)	$ (207)	$ 169,110
Issuance of common stock upon exercise of stock options and employee stock purchase plan	72,663	—	220	—	—	220
Issuance of common stock	5,564	—	35	—	—	35
Issuance of restricted stock units	11,821	—	—	—	—	—
Stock-based compensation expense	—	—	10,113	—	—	10,113
Unrealized gain on marketable securities	—	—	—	—	127	127
Net loss	—	—	—	(57,878)	—	(57,878)
Balances at December 31, 2016	27,332,551	27	359,329	(237,549)	(80)	121,727
Issuance of common stock upon exercise of stock options and employee stock purchase plan	136,992	—	195	—	—	195
Issuance of restricted stock units	19,914	—	—	—	—	—
Stock-based compensation expense	—	—	8,301	—	—	8,301
Unrealized gain on marketable securities	—	—	—	—	22	22
Net loss	—	—	—	(52,028)	—	(52,028)
Balances at December 31, 2017	27,489,457	27	367,825	(289,577)	(58)	78,217
Issuance of common stock, net of issuance costs	9,200,000	9	64,401	—	—	64,410
Issuance of common stock upon exercise of stock options and employee stock purchase plan	578,842	1	2,359	—	—	2,360
Issuance of restricted stock units	18,922	—	—	—	—	—
Stock-based compensation expense	—	—	9,627	—	—	9,627
Unrealized gain on marketable securities	—	—	—	—	25	25
Net loss	—	—	—	(61,368)	—	(61,368)
Balances at December 31, 2018	37,287,221	$ 37	$ 444,212	$ (350,945)	$ (33)	$ 93,271

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

ZAFGEN, INC.

CONSOLIDATED STATEMENTS OF CASH FLOWS
(In thousands)

	Year Ended December 31,		
	2018	**2017**	**2016**
Cash flows from operating activities:			
Net loss	$ (61,368)	$ (52,028)	$ (57,878)
Adjustments to reconcile net loss to net cash used in operating activities:			
Stock-based compensation expense	9,627	8,301	10,113
Non-cash interest expense	—	13	43
Depreciation expense	261	188	212
Loss on disposal of research and development equipment	—	—	328
Unrealized foreign currency transaction losses (gains)	76	(46)	6
Premium on marketable securities, net	(6)	(359)	(340)
Amortization of (discount) premium on marketable securities	(670)	246	1,037
Changes in operating assets and liabilities:			
Prepaid expenses and other current assets	199	(569)	413
Tax incentive receivable	(666)	(553)	970
Accounts payable	432	448	(4,625)
Accrued expenses	628	575	(2,254)
Net cash used in operating activities	(51,487)	(43,784)	(51,975)
Cash flows from investing activities:			
Proceeds from sales and maturities of marketable securities	110,388	150,213	188,600
Purchases of marketable securities	(117,147)	(114,511)	(136,528)
Purchases of property and equipment	(108)	(55)	(660)
Deposits for leased property	—	—	35
Net cash (used in) provided by investing activities	(6,867)	35,647	51,447
Cash flows from financing activities:			
Proceeds from issuance of notes payable	—	20,000	—
Repayments of notes payable	—	(3,633)	(2,935)
Proceeds from exercise of common stock options and employee stock purchase plan	2,360	195	220
Proceeds from public offerings, net of commissions and underwriting discounts	64,860	—	—
Payments of public offering costs	(312)	—	—
Net cash provided by (used in) financing activities	66,908	16,562	(2,715)
Net increase (decrease) in cash and cash equivalents	8,554	8,425	(3,243)
Cash and cash equivalents at beginning of period	40,777	32,352	35,595
Cash and cash equivalents at end of period	$ 49,331	$ 40,777	$ 32,352
Supplemental disclosure of non-cash investing and financing activities:			
Public offering costs included in accounts payable	$ 138	$ —	$ —
Supplemental disclosure of cash flow information:			
Cash paid for interest	$ 1,144	$ 141	$ 388

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

1. Nature of the Business and Basis of Presentation

Zafgen, Inc., or the Company, was incorporated on November 22, 2005 under the laws of the State of Delaware. The Company is a clinical-stage biopharmaceutical company leveraging its proprietary knowledge of the methionine aminopeptidase 2 ("MetAP2") pathway to develop novel therapies for patients affected by a range of complex metabolic diseases. Zafgen has pioneered the study of MetAP2 inhibitors in both common and rare metabolic disorders, and its current disease areas of focus are type 2 diabetes, Prader-Willi syndrome ("PWS") and liver diseases. The Company's lead product candidate is ZGN-1061, a MetAP2 inhibitor in Phase 2 clinical development with unique properties that maximize impact on metabolic parameters relevant to the treatment of type 2 diabetes and other related metabolic disorders. In January 2018, the Company announced advancement of its highly optimized MetAP2 development candidate ZGN-1258, and in the first quarter of 2018, initiated investigational new drug application ("IND") enabling nonclinical efforts for evaluation in the treatment of people affected by PWS. In March 2019, we announced our decision to suspend plans to file an IND for ZGN-1258 in order to evaluate ZGN-1258 following an unexpected finding in muscle tissue in rodent toxicology studies. During the fourth quarter of 2018 the Company announced that ZGN-1345, an orally dosed MetAP2 inhibitor specifically targeting the liver, has been formally advanced to development candidate stage. The Company is subject to risks common to companies in the biotechnology industry including, but not limited to, new technological innovations, protection of proprietary technology, dependence on key personnel, compliance with government regulations and the need to obtain additional financing. Product candidates currently under development will require significant additional research and development efforts, including extensive nonclinical and clinical testing and regulatory approval, prior to commercialization. These efforts require significant amounts of additional capital, adequate personnel infrastructure, and extensive compliance-reporting capabilities.

The Company's product candidates are all in the research and development stage. There can be no assurance that the Company's research and development will be successfully completed, that adequate protection for the Company's intellectual property will be obtained, that any product candidates developed will obtain necessary government regulatory approval or that any approved products will be commercially viable. Even if the Company's product development efforts are successful, it is uncertain when, if ever, the Company will generate significant revenue from product sales. The Company operates in an environment of rapid change in technology and substantial competition from pharmaceutical and biotechnology companies. In addition, the Company is dependent upon the services of its employees and consultants.

The Company has incurred losses and negative cash flows from operations since its inception. As of December 31, 2018, the Company had an accumulated deficit of $350.9 million. From its inception through December 31, 2018, the Company received net proceeds of $397.9 million from the sales of redeemable convertible preferred stock, the issuance of convertible promissory notes, the proceeds from its initial public offering ("IPO") in June 2014 and its follow-on offerings in January 2015 and July 2018. On July 2, 2018, the Company completed a public offering of its common stock, which resulted in the sale of 9,200,000 shares at a price of $7.50 per share, resulting in net proceeds of approximately $64.6 million after deducting underwriting discounts and commissions, as well as offering costs. As disclosed in Note 6 to the consolidated financial statements, the Company has a term loan with an aggregate principal balance of $20.0 million as of December 31, 2018. The loan agreement requires that the Company maintain certain minimum liquidity at all times, which as of December 31, 2018, was approximately $21.0 million. If the minimum liquidity covenant is not met, the Company may be required to repay the loans prior to scheduled maturity dates. Until such time, if ever, as the Company can generate substantial product revenue, the Company expects to finance its cash needs through a combination of equity offerings, debt financings, collaborations, strategic alliances, licensing arrangements and other sources of funding.

Based on its current operating plans, the Company believes its cash, cash equivalents and marketable securities of $118.1 million as of December 31, 2018 will be sufficient to fund its anticipated level of operations, capital expenditures and satisfy debt repayments for a period of at least 12 months from the issuance date of this Annual Report. The Company expects to generate operating losses for the foreseeable future. If the Company is unable to raise additional funds through equity or debt financings, the Company may be required to delay, limit, reduce or terminate product development or future commercialization efforts or grant rights to develop and market products or product candidates that the Company would otherwise prefer to develop and market itself.

The consolidated financial statements include the accounts of the Company and its wholly owned subsidiaries Zafgen Securities Corporation, Zafgen Australia Pty Limited, and Zafgen Animal Health, LLC. All intercompany balances and transactions have been eliminated.

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

2. Summary of Significant Accounting Policies

Use of Estimates

The preparation of financial statements in conformity with GAAP requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities, the disclosure of contingent assets and liabilities as of the date of the consolidated financial statements, and the reported amounts of expenses during the reporting periods. Significant estimates and assumptions reflected in these consolidated financial statements include, but are not limited to, the accrual of research and development expenses and the valuation of stock-based awards. Estimates are periodically reviewed in light of changes in circumstances, facts and experience. Actual results could differ from the Company's estimates.

Cash Equivalents

The Company considers all short-term, highly liquid investments with original maturities of ninety days or less at acquisition date to be cash equivalents. Cash equivalents, which consist of money market funds, U.S. government securities, corporate bonds, and commercial paper, are stated at fair value.

Concentration of Credit Risk and of Significant Suppliers

Financial instruments that potentially expose the Company to concentrations of credit risk consist primarily of cash, cash equivalents and marketable securities. The Company has all cash, cash equivalents and marketable securities balances at three accredited financial institutions in amounts that exceed federally insured limits. The Company does not believe that it is subject to unusual credit risk beyond the normal credit risk associated with commercial banking relationships.

The Company is dependent on third-party manufacturers to supply products for research and development activities in its programs. In particular, the Company relies and expects to continue to rely on a small number of manufacturers to supply it with its requirements for the active pharmaceutical ingredients and formulated drugs related to these programs. These programs could be adversely affected by a significant interruption in the supply of active pharmaceutical ingredients and formulated drugs.

Marketable Securities

Marketable securities consist of investments with original maturities greater than ninety days. The Company has classified its investments with maturities beyond one year as short term, based on their highly liquid nature and because such marketable securities represent the investment of cash that is available for current operations. The Company classifies its marketable securities as available-for-sale. Accordingly, these investments are recorded at fair value, which is based on quoted market prices. Unrealized gains and losses are reported as a component of accumulated other comprehensive loss in stockholders' equity. Realized gains and losses and declines in value judged to be other than temporary are included as a component of other income (expense), net, based on the specific identification method. When determining whether a decline in value is other than temporary, the Company considers various factors, including whether the Company has the intent to sell the security, and whether it is more likely than not that the Company will be required to sell the security prior to recovery of its amortized cost basis. Fair value is determined based on quoted market prices.

Deferred Offering Costs

The Company capitalizes certain legal, accounting and other third-party fees that are directly associated with in-process equity financings as other assets until such financings are consummated. After consummation of the equity financing, these costs are recorded in stockholders' equity as a reduction of additional paid-in capital generated as a result of the offering or as a reduction to the carrying value of preferred stock issued.

Property and Equipment

Property and equipment are stated at cost less accumulated depreciation. Depreciation expense is recognized using the straight-line method over a three or five-year estimated useful life for equipment, furniture and fixtures and office equipment. Leasehold improvements are amortized over the shorter of the asset life or the term of the lease agreement. Expenditures for repairs and maintenance of assets are charged to expense as incurred. Upon retirement or sale, the cost and related

accumulated depreciation of assets disposed of are removed from the accounts and any resulting gain or loss is included in loss from operations.

Impairment of Long-Lived Assets

Long-lived assets consist of property and equipment. Long-lived assets to be held and used are tested for recoverability whenever events or changes in business circumstances indicate that the carrying amount of the assets may not be fully recoverable. Factors that the Company considers in deciding when to perform an impairment review include significant underperformance of the business in relation to expectations, significant negative industry or economic trends, and significant changes or planned changes in the use of the assets. If an impairment review is performed to evaluate a long-lived asset for recoverability, the Company compares forecasts of undiscounted cash flows expected to result from the use and eventual disposition of the long-lived asset to its carrying value. An impairment loss would be recognized when estimated undiscounted future cash flows expected to result from the use of an asset are less than its carrying amount. The impairment loss would be based on the excess of the carrying value of the impaired asset over its fair value, determined based on discounted cash flows. To date, the Company has not recorded any impairment losses on long-lived assets.

Research and Development Costs

Research and development costs are expensed as incurred. Included in research and development expenses are wages, stock-based compensation and benefits of employees, third-party license fees and milestones and other operational costs related to the Company's research and development activities, including facility-related expenses and external costs of outside vendors engaged to conduct nonclinical studies, manufacturing activities, and clinical trials. The Company records research and development expenses net of any research and development tax incentives the Company is entitled to receive from government authorities.

Research Contract Costs and Accruals

The Company has entered into various research and development contracts with research institutions and other companies both inside and outside of the United States. These agreements are generally cancelable, and related payments are recorded as research and development expenses as incurred. The Company records accruals for estimated ongoing research costs. When evaluating the adequacy of the accrued liabilities, the Company analyzes progress of the studies, including the phase or completion of events, invoices received and contracted costs. Significant judgments and estimates are made in determining the accrued balances at the end of any reporting period. Actual results could differ from the Company's estimates. The Company's historical accrual estimates have not been materially different from the actual costs.

Patent Costs

All patent-related costs incurred in connection with filing and prosecuting patent applications are recorded as general and administrative expenses as incurred, as recoverability of such expenditures is uncertain.

Accounting for Stock-Based Compensation

The Company measures all stock-based awards granted to employees and directors based on the fair value on the date of grant using the Black-Scholes option-pricing model. Compensation expense of those awards is recognized over the requisite service period, which is generally the vesting period of the respective award. Typically, the Company issues awards with only service-based and market-based vesting conditions and records the expense for these awards using the straight-line method. The Company accounts for forfeitures as they occur.

For stock-based awards granted to non-employee consultants, compensation expense is recognized over the period during which services are rendered by such consultants until completed. At the end of each financial reporting period prior to completion of the service, the fair value of these awards is re-measured using the then-current fair value of the Company's common shares and updated assumption inputs in the Black-Scholes option-pricing model.

The Company classifies stock-based compensation expense in its consolidated statements of operations and comprehensive loss in the same manner in which the award recipient's payroll costs are classified or in which the award recipient's service payments are classified.

Income Taxes

The Company accounts for income taxes using the asset and liability method, which requires the recognition of deferred tax assets and liabilities for the expected future tax consequences of events that have been recognized in the consolidated financial statements or in the Company's tax returns. Deferred taxes are determined based on the difference between the financial statement and tax basis of assets and liabilities using enacted tax rates in effect in the years in which the differences are expected to reverse. Changes in deferred tax assets and liabilities are recorded in the provision for income taxes. The Company 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 a charge to income tax expense. Potential for recovery of deferred tax assets is evaluated by estimating the future taxable profits expected and considering prudent and feasible tax planning strategies.

The Company accounts for uncertainty in income taxes recognized in the consolidated financial statements by applying a two-step process to determine the amount of tax benefit to be recognized. First, the tax position must be evaluated to determine the likelihood that it will be sustained upon external examination by the taxing authorities. If the tax position is deemed more-likely-than-not to be sustained, the tax position is then assessed to determine the amount of benefit to recognize in the consolidated financial statements. The amount of the benefit that may be recognized is the largest amount that has a greater than 50% likelihood of being realized upon ultimate settlement. The provision for income taxes includes the effects of any resulting tax reserves, or unrecognized tax benefits, that are considered appropriate as well as the related net interest and penalties.

Segment Data

The Company manages its operations as a single segment for the purposes of assessing performance and making operating decisions. The Company is a biopharmaceutical company dedicated to significantly improving the health and well-being of patients affected by both rare and prevalent metabolic diseases including type 2 diabetes, PWS, liver diseases and potentially other metabolically related disorders. No revenue has been generated since inception, and all tangible assets are held in the United States.

Comprehensive Loss

Comprehensive loss includes net loss as well as other changes in stockholders' equity that result from transactions and economic events other than those with stockholders. For the years ended December 31, 2018, 2017 and 2016, the Company's only element of other comprehensive loss was unrealized gain or (loss) on marketable securities.

Net Loss Per Share

Basic net loss per share is computed by dividing the net loss attributable to common stockholders by the weighted average number of common shares outstanding for the period. Diluted net loss per share attributable to common stockholders is computed by dividing the diluted net loss attributable to common stockholders by the weighted average number of common shares, including potential dilutive common shares assuming the dilutive effect of outstanding stock options and unvested restricted common shares, as determined using the treasury stock method. For periods in which the Company has reported net losses, diluted net loss per common share attributable to common stockholders is the same as basic net loss per common share attributable to common stockholders, since dilutive common shares are not assumed to have been issued if their effect is antidilutive.

Recently Issued and Adopted Accounting Pronouncements

In February 2016, the Financial Accounting Standards Board (the "FASB") issued ASU No. 2016-02, Leases, and in July 2018, the FASB issued ASU No. 2018-11, Leases (Topic 842): *Targeted Improvements.* The new leasing standards generally require lessees to recognize operating and financing lease liabilities and corresponding right-of-use assets on the consolidated balance sheet and to provide enhanced disclosures surrounding the amount, timing and uncertainty of cash flows arising from leasing arrangements. The Company will adopt the new standard effective January 1, 2019 and will not restate comparative periods. Presentation of leases within the consolidated statements of operations and comprehensive loss and consolidated statements of cash flows will be generally consistent with the current lease accounting guidance. The Company will elect the package of practical expedients permitted under the transition guidance and as such, the adoption of this ASU will not change the classification of any of the Company's leases. The Company will elect to combine lease and non-lease components, elect not to record leases with an initial term of 12 months or less on the balance sheet and recognize the associated lease payments in the consolidated statements of operations on a straight-line basis over the lease term. The Company is still assessing its existing lease contracts and the impact of the new leasing standards on its consolidated results of operations, financial position and disclosures. The Company currently expects the impact of adoption of the new leasing standards will have a material impact to the Company's consolidated balance sheet in recognizing additional lease liabilities and right-of-use assets as of January 1, 2019 related to the Company's operating leases. The Company does not expect that the new standard will have a material impact on its consolidated statements of operations or cash flows.

In August 2016, the FASB issued ASU No. 2016-15, *Statement of Cash Flows: Classification of Certain Cash Receipts and Cash Payments*. This guidance addresses the presentation and classification of certain cash receipts and cash payments in the statement of cash flows. This standard was effective for the Company in 2018. The adoption of this guidance had no impact on the Company's consolidated financial statements as of and for the year ended December 31, 2018.

In May 2017, the FASB issued ASU No. 2017-09, *Compensation – Stock Compensation: Scope of Modification Accounting*. This guidance addresses which changes to the terms or conditions of a share-based payment award require an entity to apply modification accounting. This standard was effective for the Company in 2018. The adoption of this guidance had no impact on the Company's consolidated financial statements as of and for the year ended December 31, 2018.

In June 2018, the FASB issued ASU No. 2018-07, *Compensation—Stock Compensation (Topic 718): Improvements to Nonemployee Share-Based Payment Accounting*. This ASU is intended to simplify aspects of share-based compensation issued to non-employees by making the guidance consistent accounting for employee share-based compensation. ASU 2018-07 is effective for annual periods beginning after December 15, 2018 and interim periods within those annual periods, with early adoption permitted. The Company is evaluating the effect that this guidance will have on its consolidated financial statements.

3. Fair Value Measurements and Marketable Securities

Fair Value Measurements

The following tables present information about the Company's financial assets that have been measured at fair value as of December 31, 2018 and 2017 and indicate the fair value of the hierarchy of the valuation inputs utilized to determine such fair value. In general, fair values determined by Level 1 inputs utilize quoted prices (unadjusted) in active markets for identical assets or liabilities. Fair value determined by Level 2 inputs utilize observable inputs other than Level 1 prices, such as quoted prices for similar assets or liabilities, quoted market prices in markets that are not active or other inputs that are observable or can be corroborated by observable market data for substantially the full term of the related assets or liabilities. Fair values determined by Level 3 inputs are unobservable data points for the asset or liability, and include situations where there is little, if any, market activity for the asset or liability. During the years ended December 31, 2018 and 2017, there were no transfers between Level 1 and Level 2 financial assets.

The following tables summarize the Company's cash equivalents and marketable securities as of December 31, 2018 and 2017:

	December 31, 2018			
	Total	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
	(in thousands)			
Cash equivalents:				
Money market funds	$ 40,231	$ 40,231	$ —	$ —
Commercial paper	4,979	—	4,979	—
Total cash equivalents	45,210	40,231	4,979	—
Marketable securities:				
Commercial paper	38,911	—	38,911	—
Corporate bonds	25,830	—	25,830	—
U.S. Government securities	3,994	—	3,994	—
Total marketable securities	68,735	—	68,735	—
Total cash equivalents and marketable securities	$ 113,945	$ 40,231	$ 73,714	$ —

	December 31, 2017			
	Total	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
	(in thousands)			
Cash equivalents:				
Money market funds	$ 15,802	$ 15,802	$ —	$ —
Commercial paper	998	—	998	—
Corporate bonds	549	—	549	—
Total cash equivalents	17,349	15,802	1,547	—
Marketable securities:				
Corporate bonds	50,844	—	50,844	—
Commercial paper	9,951	—	9,951	—
Certificates of deposit	480	—	480	—
Total marketable securities	61,275	—	61,275	—
Total cash equivalents and marketable securities	$ 78,624	$ 15,802	$ 62,822	$ —

The carrying amounts reflected in the consolidated balance sheets for tax incentive receivable, accounts payable, and accrued expenses approximate fair value due to their short-term maturities. The carrying value of the Company's outstanding notes payable approximates fair value (a Level 2 fair value measurement), reflecting interest rates currently available to the Company.

Marketable Securities

The following tables summarize the Company's marketable securities as of December 31, 2018 and 2017:

	December 31, 2018			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value
	(in thousands)			
Assets:				
Commercial paper (due within 1 year)	38,921	—	(10)	38,911
Corporate bonds (due within 1 year)	$ 25,851	$ 3	$ (24)	$ 25,830
U.S. Government securities (due within 1 year)	3,995	—	(1)	3,994
	$ 68,767	$ 3	$ (35)	$ 68,735

	December 31, 2017			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value
	(in thousands)			
Assets:				
Corporate bonds (due within 1 year)	$ 50,892	$ —	$ (48)	$ 50,844
Commercial paper (due within 1 year)	9,961	—	(10)	9,951
Certificates of deposit (due within 1 year)	480	—	—	480
	$ 61,333	$ —	$ (58)	$ 61,275

4. Property and Equipment, net

Property and equipment, net consisted of the following as of December 31, 2018 and 2017:

		December 31,	
	Useful Life	2018	2017
		(in thousands)	
Office equipment	3-5 years	$ 348	$ 421
Furniture and fixtures	5 years	156	194
Equipment	5 years	6	6
Leasehold improvements	*	415	415
		925	1,036
Less: Accumulated depreciation		(550)	(508)
		$ 375	$ 528

* shorter of asset life or lease term

Depreciation expense was $0.3 million, $0.2 million and $0.2 million for the years ended December 31, 2018, 2017 and 2016, respectively.

5. Accrued Expenses

Accrued expenses consisted of the following as of December 31, 2018 and 2017:

	December 31,	
	2018	2017
	(in thousands)	
Accrued payroll and related expenses	$ 2,291	$ 2,229
Accrued research and development expenses	1,526	1,647
Accrued professional fees	221	292
Accrued other	223	105
	$ 4,261	$ 4,273

6. Notes Payable

On December 29, 2017, the Company entered into a loan and security agreement with Silicon Valley Bank (the "Term Loan"). The Term Loan provided for borrowings of $20.0 million. On December 29, 2017, the Company received proceeds of $20.0 million from the issuance of a promissory note. The promissory note issued under the Term Loan is collateralized by substantially all of the Company's personal property, other than its intellectual property.

Upon entering into this Term Loan, the Company is obligated to make monthly, interest-only payments until March 29, 2019 and, thereafter, to pay 33 consecutive, equal monthly installments of principal and interest from April 1, 2019 through December 1, 2021. The outstanding Term Loan bears a variable annual interest rate of 1.25% above the prime rate, which at December 31, 2018 was 5.5%. In addition, a final payment equal to 8.0% of the Term Loan is due upon the earlier of the maturity date, acceleration of the Term Loan or prepayment of all or part of the Term Loan. The Company accrues the final payment amount of $1.6 million, to outstanding debt by charges to interest expense using the effective-interest method from the date of issuance through the maturity date. The effective annual interest rate of the outstanding debt under the Term Loan is approximately 9.9% as of December 31, 2018.

Additionally, the Company, as the borrower, is required to maintain a minimum cash, cash equivalents and marketable securities balance at Silicon Valley Bank of no less than 105% of the total outstanding principal balance of the Term Loan, which as of December 31, 2018 and 2017 was $21.0 million.

Further, as of 45 days after the Term Loan was entered in, the Company must maintain a balance of unrestricted cash, cash equivalents and marketable securities at Silicon Valley Bank in an amount not less than the greater of (i) $55.0 million and (ii) sixty-five percent (65%) of all the Company's cash, cash equivalents and marketable securities. If the Company does not meet this requirement it will not be considered an event of default provided it immediately secures 87.5% of the principal balance in a restricted cash account.

There are negative covenants restricting the Company's activities, including limitations on dispositions, mergers or acquisitions; encumbering or granting a security interest in its intellectual property; incurring indebtedness or liens; paying dividends; making certain investments; permit the aggregate value of cash maintained by its Australian subsidiary not to exceed $4.0 million and certain other business transactions.

The Term Loan also includes events of default, the occurrence and continuation of any of which provides the lenders the right to exercise remedies against the Company and the collateral securing the loans under the Term Loan, including cash in the amount of the outstanding balance. These events of default include, among other things, failure to pay any amounts due under the Term Loan, insolvency, the occurrence of a material adverse event, the occurrence of any default under certain other indebtedness and a final judgment against the Company in an amount greater than $0.3 million.

As of December 31, 2017, the Company had fully repaid all outstanding amounts due under a loan and security agreement with Oxford Finance LLC and Midcap Financial (the "2014 Credit Facility") entered into in March 2014.

As of December 31, 2018 and 2017, notes payable consist of the following:

	December 31,	
	2018	2017
	(in thousands)	
Notes payable	$ 20,000	$ 20,000
Less: current portion	(5,455)	—
Notes payable, net of current portion	14,545	20,000
Accretion related to final payment	640	—
Notes payable, long term	$ 15,185	$ 20,000

As of December 31, 2018, the estimated future principal payments due are as follows:

Year Ending December 31, (in thousands)	
2019	$ 5,455
2020	7,273
2021	7,272
	$ 20,000

During the years ended December 31, 2018 and 2017, the Company recognized $1.9 million and less than $0.1 million, respectively, of interest expense related to the Term Loan. During the years ended December 31, 2017 and 2016, the Company recognized $0.2 million and $0.5 million, respectively, of interest expense related to the 2014 Credit Facility.

7. Stockholders' Equity

On July 2, 2018, the Company completed a public offering of its common stock, which resulted in the sale of 9,200,000 shares at a price of $7.50 per share, resulting in net proceeds of approximately $64.6 million after deducting underwriting discounts and commissions, as well as offering costs.

On November 9, 2018, the Company entered into a sales agreement (the "Sales Agreement") with Cowen and Company, LLC ("Cowen"), to sell shares of the Company's common stock, with aggregate gross sales proceeds of up to $50.0 million, from time to time, through an at-the-market equity offering program under which Cowen will act as its sales agent (the "ATM Offering Program"). Cowen is entitled to compensation for its services equal to 3.0% of the gross proceeds of any shares of common stock sold through Cowen under the Sales Agreement. The Company has no obligation to sell any shares under the Sales Agreement, and may at any time suspend solicitation and offers under the Sales Agreement. The shares will be issued pursuant to the Company's Registration Statement on Form S-3 filed on August 9, 2017 with the Securities and Exchange Commission ("SEC"). The Company filed a prospectus supplement, dated November 9, 2018, with the SEC in connection with the offer and sale of the shares pursuant to the Sales Agreement. As of December 31, 2018, the Company has not sold shares under the Sales Agreement.

As of December 31, 2018 and 2017, the Company's Certificate of Incorporation, as amended and restated, authorizes the Company to issue 5,000,000 shares of $0.001 par value preferred stock. The rights, preferences, restrictions, qualifications and limitations of such stock are to be determined by the Company's board of directors.

As of December 31, 2018 and 2017, the Company's Certificate of Incorporation, as amended and restated, authorizes the Company to issue 115,000,000 shares of $0.001 par value common stock.

8. Stock-Based Awards

Stock Option Plan

The Company's 2014 Stock Option and Incentive Plan (the "2014 Plan") provides for the grant of stock options, stock appreciation rights, restricted stock awards, restricted stock units, unrestricted stock awards, performance-share awards, cash-based awards and dividend equivalent rights to employees, members of the board of directors and consultants of the Company. The number of shares initially reserved for issuance under the 2014 Plan was 2,168,221 shares of common stock. The number of shares reserved for issuance may be increased by the number of shares under the previously authorized 2006 Stock Option Plan that are not needed to fulfill the Company's obligations for awards issued under the 2006 Stock Option Plan as a result of forfeiture, expiration, cancellation, termination or net issuances of awards thereunder. The number of shares of common stock that may be issued under the 2014 Plan is also subject to increase on the first day of each fiscal year by the lesser of (i) 4% of the Company's outstanding shares of common stock as of that date, or (ii) an amount determined by the board of directors. As of December 31, 2018, 2,499,951 shares are available for grant under the 2014 Plan, including 1,099,578 shares automatically added to the 2014 Stock Option Plan on January 1, 2018.

Stock Option Grants

Option Grants with time-based vesting conditions

During the years ended December 31, 2018, 2017 and 2016, the Company granted 1,823,386, 1,214,874 and 1,527,559 stock options, respectively, under the 2014 Plan. The vesting of these awards is time-based and the restrictions typically lapse over periods of three to four years. Stock options were granted with exercise prices equal to the fair value of the Company's common stock on the date of grant. The Company bases fair value of common stock on the quoted market price of the Company's common stock. During the years ended December 31, 2018 and 2017 the Company granted 225,000 and 550,000 options, respectively, with time-based vesting as inducement grants outside of the 2014 Plan in accordance with NASDAQ Listing Rule 5635(c)(4). These stock options have a ten-year term and an exercise price equal to the closing price of the Company's common stock on the grant date. The options vest as to 25% of the shares on the first anniversary of the grant date and the remainder in equal monthly installments thereafter over a 3-year period.

The fair value of each service-based stock option grant to employees and directors is estimated on the date of grant using the Black-Scholes option-pricing model. The Company estimates its expected volatility using a weighted average of the historical volatility of publicly-traded peer companies and its own common stock since its IPO in June 2014, and expects to continue to do so until such time as it has adequate historical data regarding the volatility of its own traded stock price for the duration of the expected term. The expected term of the Company's stock options has been determined utilizing the "simplified" method for awards that qualify as "plain-vanilla" options. The risk-free interest rate is determined by reference to the U.S. Treasury yield curve in effect at the time of grant of the award for time periods approximately equal to the expected term of the award. Expected dividend yield is based on the fact that the Company has never paid cash dividends and does not expect to pay any cash dividends in the foreseeable future. The assumptions that the Company used to determine the fair value of the stock options granted to employees and directors are as follows, presented on a weighted average basis:

	2018	2017	2016
Risk-free interest rate	2.77%	2.10%	1.40%
Expected term (in years)	6.17	6.17	6.18
Expected volatility	100%	93%	87%
Expected dividend yield	0%	0%	0%

The following table summarizes the Company's stock option activity described above, since December 31, 2017:

	Shares Issuable Under Options	Weighted Average Exercise Price	Average Remaining Contractual Term	Aggregate Intrinsic Value
			(in years)	(in thousands)
Outstanding as of December 31, 2017	4,494,201	$ 10.12	7.8	$ 3,251
Granted	2,048,386	$ 7.59		
Exercised	(532,661)	$ 4.12		
Forfeited	(985,555)	$ 14.58		
Outstanding as of December 31, 2018	5,024,371	$ 8.85	7.6	$ 3,143
Options exercisable as of December 31, 2018	2,421,674	$ 11.22	6.1	$ 2,240

The aggregate intrinsic value was calculated based on the positive differences between the market value of the Company's common stock and the exercise prices of the options. The aggregate intrinsic value of service-based stock options exercised was $1.6 million, $0.3 million and $0.1 million during the years ended December 31, 2018, 2017 and 2016, respectively.

The Company received cash proceeds from the exercise of stock options of $2.2 million, $0.1 million, and less than $0.1 million during the years ended December 31, 2018, 2017 and 2016, respectively.

The weighted average grant-date fair value of service-based stock options granted to employees and directors during the years ended December 31, 2018, 2017 and 2016 was $6.08, $2.91 and $4.86, per share, respectively.

As of December 31, 2018 and 2017, there were outstanding unvested service-based stock options held by nonemployees for the purchase of 45,209 and 77,567 shares of common stock, respectively.

Option Grants with market-based vesting conditions

In October 2017, the Company granted 687,500 common stock options that vest on the third anniversary of the grant date upon achievement by the Company of minimum common stock prices for 20 consecutive days during the Earning Period, the ("Price Target Options"). The Earning Period is defined as the period between the first anniversary of the grant date and the third anniversary of the grant date. Of the 687,500 Price Target Options granted in 2017, 137,500 were granted under the 2014 Stock Plan and 550,000 were granted to the newly-hired Chief Executive Officer as an inducement grant outside of the 2014 Plan in accordance with NASDAQ Listing Rule 5635(c)(4). These stock options have a ten-year term and an exercise price equal to the closing price of the Company's common stock on the grant date. In August 2018, the 137,500 shares granted under the 2014 Stock Plan were forfeited.

The number of Price Target Options that will vest upon achievement of the target will vary based on the level of achievement from a maximum of 200% of the target shares to a threshold of 50% of the target shares, with no vesting, absent certain circumstances, if the threshold requirement is not achieved or the employee is no longer with the Company at the end of the three-year period. The Price Target Options are valued using Monte Carlo simulation models. The number of options expected to vest, based on achievement of the specified market condition, is factored into the grant date Monte Carlo valuations for the Price Target Options. Compensation expense is recognized ratably over the attribution period.

The assumptions that the Company used to determine the fair value of the Price Target Options granted to employees were as follows, presented on a weighted average basis:

	2017
Risk-free interest rate	2.24%
Expected term (in years)	6.30
Expected volatility	95%
Expected dividend yield	0%

The Price Target Options had a grant date total fair value of $3.1 million and a weighted average fair value of $4.56 per share. As of December 31, 2018, the 550,000 Price Target Options had an aggregate intrinsic value of $0.9 million and a remaining contractual term of 8.77 years.

Restricted Stock Units

The Company has granted restricted stock units with time-based vesting conditions. The Company values restricted stock units on the grant-date using the market price of the Company's common stock. The aggregate intrinsic value of restricted stock units that vested during the years ended December 31, 2018, 2017 and 2016 was $0.2 million, $0.1 million and $0.1 million respectively, calculated as the fair value of the Company's common stock on the date it vests. During the years ended December 31, 2018, 2017 and 2016, the Company granted 17,856, 22,128 and 13,273 restricted stock units, respectively, all of which vested during 2018, 2017 and 2016, respectively, at a weighted average grant-date fair value of $5.18, $4.18 and $7.91, respectively. As of December 31, 2018 and 2017, there were no unvested restricted stock units outstanding.

2014 Employee Stock Purchase Plan

The Company has a 2014 Employee Stock Purchase Plan (the "ESPP") under which a total of 265,000 shares of common stock were reserved for issuance. During both 2018 and 2017 there were two offering periods, January 1 through June 30 and July 1 through December 31. The per share purchase price for offerings is equal to the lesser of 85% of the closing market price of the Company's common stock on the first day or last day of the offering period. The Company issued 46,181 and 43,781 shares during the years ended December 31, 2018 and 2017, respectively. As of December 31, 2018 and 2017, there are 129,835 and 176,016 shares, respectively, of common stock available for issuance to participating employees under the ESPP.

Stock-based Compensation

The Company recorded stock-based compensation expense related to stock options and restricted common stock in the following expense categories within its consolidated statements of operations:

	Year Ended December 31,		
	2018	2017	2016
	(in thousands)		
Research and development	$ 5,476	$ 4,138	$ 3,543
General and administrative	4,151	4,163	6,390
	$ 9,627	$ 8,301	$ 9,933

In addition, during the year ended December 31, 2016, in connection with its strategic restructuring further discussed in Note 14, the Company recorded a one-time, non-cash stock option modification expense of $0.2 million, which is included in the stock-based compensation expense line items of both the consolidated statements of cash flows and the consolidated statements of changes in stockholders' equity.

As of December 31, 2018, the Company had unrecognized stock-based compensation expense related to its unvested service-based stock option awards of $10.8 million, which is expected to be recognized over the remaining weighted average vesting period of 2.2 years.

As of December 31, 2018, the Company had unrecognized stock-based compensation expense related to its unvested market-based stock option awards of $1.7 million, which is expected to be recognized over the remaining weighted average vesting period of 1.8 years.

9. Net Loss Per Share

Basic and diluted net loss per share was calculated as follows:

	Year Ended December 31,		
	2018	2017	2016
	(in thousands, except per share data)		
Basic and diluted net loss per share:			
Numerator:			
Net loss	$ (61,368)	$ (52,028)	$ (57,878)
Denominator:			
Weighted average common shares outstanding, basic and diluted	32,228,721	27,433,239	27,297,934
Net loss per share, basic and diluted	$ (1.90)	$ (1.90)	$ (2.12)

The Company excluded the following common stock equivalents, outstanding as of December 31, 2018, 2017 and 2016, from the computation of diluted net loss per share for the years ended December 31, 2018, 2017 and 2016 because they had an anti-dilutive impact due to the net loss incurred for the periods:

	As of December 31,		
	2018	2017	2016
Options to purchase common stock	5,024,371	4,494,201	3,115,003

10. Commitments and Contingencies

Leases

The Company has a lease for office space in Boston, Massachusetts, effective as of July 28, 2014, with a term expiring July 31, 2020. In March 2015, the Company entered into an operating lease for additional office space in Boston, Massachusetts, effective as of April 15, 2015, with a term expiring on July 31, 2020, and an option to extend this lease for three additional years. In addition, with the landlord's consent, the Company has subleased 2,976 square feet of office space in Boston, Massachusetts to an unrelated third party beginning on January 1, 2017 and expiring on June 30, 2020, and the Company expects to receive approximately $0.2 million in sublease rental income from January 1, 2019 through the end of the sublease term. In October 2015, the Company entered into an operating lease for office space in San Diego, California, effective as of October 1, 2015, with a term expiring on September 30, 2019, and an option to extend this lease for five additional years.

Future minimum lease payments for its operating leases as of December 31, 2018 were as follows:

Year Ending December 31, **(in thousands)**	
2019	$ 464
2020	226
2021	—
2022	—
	$ 690

During the years ended December 31, 2018, 2017 and 2016, the Company recognized $0.4 million, $0.3 million and $0.4 million, respectively, of rental expense related to office space.

Intellectual Property Licenses

The Company has acquired exclusive rights to develop patented compounds and related know-how for beloranib under two licensing agreements with two third parties in the course of its research and development activities. The licensing rights obligate the Company to make payments to the licensors for license fees, milestones, license maintenance fees and royalties. The Company is also responsible for patent prosecution costs.

As of December 31, 2018, the Company is obligated to make additional milestone payments of up to $12.3 million upon reaching certain pre-commercialization milestones, such as clinical trials and government approvals (including the U.S. Food and Drug Administration, or "FDA", approval of a New Drug application, or "NDA"), and up to $12.5 million upon reaching certain product commercialization milestones related to the development of beloranib. Under one of the license agreements, the Company is also obligated to pay up to $1.3 million with respect to each subsequent licensed product, if any, that is a new chemical entity. In addition, the Company will owe single-digit royalties on sales of commercial products developed using these licensed technologies, if any.

There were no milestones achieved during the years ended December 31, 2018, 2017 or 2016. The Company is also obligated to pay to the licensors a percentage of fees received if and when the Company sublicenses the technology. As of December 31, 2018, the Company has not yet developed a commercial product using the licensed technologies and it has not entered into any sublicense agreements for the technologies.

Indemnification Agreements

In the ordinary course of business, the Company may provide indemnification of varying scope and terms to vendors, lessors, business partners, and other parties with respect to certain matters including, but not limited to, losses arising out of breach of such agreements or from intellectual property infringement claims made by third parties. In addition, the Company has entered into indemnification agreements with members of management team and the board of directors of the Company that will require the Company, among other things, to indemnify them against certain liabilities that may arise by reason of their status or service as directors or officers. The maximum potential amount of future payments the Company could be required to make under these indemnification agreements is, in many cases, unlimited. To date, the Company has not incurred any material costs as a result of such indemnifications. The Company does not believe that the outcome of any claims under indemnification arrangements will have a material effect on its financial position, results of operations or cash flows, and it has not accrued any liabilities related to such obligations in its consolidated financial statements as of December 31, 2018.

Legal Proceedings

The Company accrues a liability for legal contingencies when it believes that it is both probable that a liability has been incurred and that the Company can reasonably estimate the amount of the loss. The Company reviews these accruals and adjusts them to reflect ongoing negotiations, settlements, rulings, advice of legal counsel and other relevant information. To the extent new information is obtained and the views on the probable outcomes of claims, suits, assessments, investigations or legal proceedings change, changes in the Company's accrued liabilities would be recorded in the period in which such determination is made. In addition, in accordance with the relevant authoritative guidance, for any matters in which the likelihood of material loss is at least reasonably possible, the Company will provide disclosure of the possible loss or range of loss. If a reasonable estimate cannot be made, however, the Company will provide disclosure to that effect. The Company expenses legal costs as they are incurred.

The Company may periodically become subject to other legal proceedings and claims arising in connection with ongoing business activities, including claims or disputes related to patents that have been issued or that are pending in the field of research on which the Company is focused. Other than the above action, the Company is not aware of any other material claims as of December 31, 2018.

11. Income Taxes

During the years ended December 31, 2018, 2017 and 2016, the Company recorded no income tax benefits for the net operating losses incurred in each year due to its uncertainty of realizing a benefit from those items.

The domestic and foreign components of loss before income taxes are as follows:

	Year Ended December 31,		
	2018	2017	2016
	(in thousands)		
Domestic	$ (58,708)	$ (49,954)	$ (57,799)
Foreign	(2,660)	(2,074)	(79)
Loss before income taxes	$ (61,368)	$ (52,028)	$ (57,878)

A reconciliation of the U.S. federal statutory income tax rate to the Company's effective income tax rate is as follows:

	Year Ended December 31,		
	2018	2017	2016
Federal statutory income tax rate	(21.0%)	(34.0%)	(34.0%)
Federal and state research and development tax credit	(4.2)	(4.1)	(2.9)
State taxes, net of federal benefit	(3.7)	(2.4)	(3.9)
Orphan drug tax credit	0.0	0.0	(1.3)
Stock compensation expense	5.1	1.5	0.7
Nondeductible Australia research and development expenses	0.9	1.4	0.0
Impact of federal rate change related to tax reform	0.0	65.2	0.0
Other items	0.0	1.2	1.3
Change in deferred tax asset valuation allowance	22.9	(28.8)	40.1
Effective income tax rate	0.0%	0.0%	0.0%

Net deferred tax assets as of December 31, 2018 and 2017 consisted of the following:

	December 31,	
	2018	2017
	(in thousands)	
Noncurrent deferred tax assets:		
Capitalized research and development expenses	$ 58,832	$ 49,325
Net operating loss carryforwards	16,728	13,848
Tax credit carryforwards	19,331	16,759
Capitalized legal expenses	1,918	1,646
Stock-based compensation	4,371	5,568
Accrued expenses	493	522
Other temporary differences	19	13
Total noncurrent deferred tax assets	101,692	87,681
Total gross deferred tax assets	101,692	87,681
Valuation allowance	(101,692)	(87,681)
Net deferred tax assets	$ —	$ —

Changes in the valuation allowance for deferred tax assets during the years ended December 31, 2018, 2017 and 2016 related primarily to changes in net operating loss carryforwards, capitalized research and development expenses and tax credit carryforwards and were as follows:

	Year Ended December 31,		
	2018	2017	2016
	(in thousands)		
Valuation allowance as of beginning of year	$ 87,681	$ 97,720	$ 74,541
Decreases recorded as benefit to income tax provision	—	(10,039)	—
Increases recorded to income tax provision	14,011	—	23,179
Valuation allowance as of end of year	$ 101,692	$ 87,681	$ 97,720

As of December 31, 2018, the Company had net operating loss carryforwards that expire for federal and state income tax purposes of $55.7 million and $48.0 million, respectively, which begin to expire in 2026 and 2030, respectively. As of December 31, 2018, the Company had net operating loss carryforwards that were generated after December 31, 2017 of $9.5 million that do not expire. As of December 31, 2018, the Company also had available tax credit carryforwards for federal and state income tax purposes of $16.6 million and $3.4 million, respectively, which begin to expire in 2026 and 2022, respectively. Utilization of the net operating loss carryforwards and tax credit carryforwards may be subject to a substantial annual limitation under Section 382 of the Internal Revenue Code of 1986 due to ownership changes that have occurred previously or that could occur in the future. These ownership changes may limit the amount of carryforwards that can be utilized annually to offset future taxable income.

In general, an ownership change, as defined by Section 382, results from transactions increasing the ownership of certain stockholders or public groups in the stock of a corporation by more than 50% over a three-year period. The Company has not conducted a study to assess whether a change of control has occurred or whether there have been multiple changes of control since inception due to the significant complexity and cost associated with such a study. If the Company has experienced a change of control, as defined by Section 382, at any time since inception, utilization of the net operating loss carryforwards or tax credit carryforwards would be subject to an annual limitation under Section 382, which is determined by first multiplying the value of the Company's stock at the time of the ownership change by the applicable long-term tax-exempt rate, and then could be subject to additional adjustments, as required. Any limitation may result in expiration of a portion of the net operating loss carryforwards or tax credit carryforwards before utilization. Further, until a study is completed and any limitation is known, no amounts are being presented as an uncertain tax position.

As of December 31, 2018 and 2017, the Company's gross deferred tax asset balance of $101.7 million and $87.7 million, respectively, was comprised principally of net operating loss carryforwards, capitalized research and development expenses and tax credit carryforwards. During the years ended December 31, 2018, 2017 and 2016, gross deferred tax assets increased (decreased) due to additional net operating loss carryforwards, research and development tax credits generated and additional research and development expenses capitalized for tax purposes and the effects of tax reform.

The Company has evaluated the positive and negative evidence bearing upon its ability to realize the deferred tax assets. Management has considered the Company's history of cumulative net losses incurred since inception and its lack of commercialization of any products or generation of any revenue from product sales since inception and has concluded that it is more likely than not that the Company will not realize the benefits of the deferred tax assets. Accordingly, a full valuation allowance has been established against the deferred tax assets as of December 31, 2018 and 2017. Management reevaluates the positive and negative evidence at each reporting period.

The Company has not recorded any amounts for unrecognized tax benefits as of December 31, 2018 and 2017.

The Company files tax returns as prescribed by the tax laws of the jurisdictions in which it operates. In the normal course of business, the Company is subject to examination by federal and state jurisdictions, where applicable. There are currently no pending income tax examinations. The Company's tax years are still open under statute from 2014 to the present. Earlier years may be examined to the extent that tax credit or net operating loss carryforwards are used in future periods. The Company's policy is to record interest and penalties related to income taxes as part of its income tax provision.

On December 22, 2017, the Tax Cuts and Jobs Act ("TCJA") was signed into U.S. law. The TCJA includes a number of changes to existing tax law, including, among other things, a permanent reduction in the federal corporate income tax rate from a top marginal rate of 35% down to a flat rate of 21%, effective as of January 1, 2018, as well as limitation of the deduction for net operating losses to 80% of annual taxable income and elimination of net operating loss carrybacks, in each

case, for losses arising in taxable years beginning after December 31, 2017 (though any such net operating losses may be carried forward indefinitely).

As a result of the TCJA, the Company was required to revalue deferred tax assets and liabilities at 21%. This revaluation in 2017 resulted in a provision of $33.8 million to income tax expense in continuing operations and a corresponding reduction in the valuation allowance. There was no impact to the Company's consolidated statements of operations and comprehensive loss as a result of the reduction in rates. The other provisions of the TCJA did not have a material impact on the Company's consolidated financial statements. In accordance with authoritative guidance issued by the SEC, the income tax effect of the TCJA represents provisional amounts for which the Company's accounting is incomplete but for which reasonable estimates were determined and recorded during the fourth quarter of 2017. The guidance provides for a measurement period, up to one year from the enactment date, in which provisional amounts may be adjusted when additional information is obtained, prepared and analyzed. During the year ended December 31, 2018, there were no changes made to the provisional amounts recognized in 2017 in connection with the enactment of the Tax Reform Act. The accounting for the income tax effects of the Tax Reform Act is complete as of December 31, 2018.

12. Retirement Plan

Effective January 1, 2018, the Company adopted a 401(k) plan for its employees. Under the terms of the plan, the Company contributes 3% of an employee's annual base salary, up to a maximum of the annual Internal Revenue Service compensation limits, for all employees. The Company terminated its Savings Incentive Match Plan, or SIMPLE IRA as of December 31, 2017.

For the year ended December 31, 2018, the Company recognized $0.3 million of expense related to its contributions to the 401(k) plan.

During the years ended December 31, 2017 and 2016, the Company recognized $0.1 million and $0.2 million, respectively, of expense related to its contributions to the SIMPLE IRA.

13. Australia Research and Development Tax Incentive

The Company's wholly owned subsidiary, Zafgen Australia Pty Limited, which conducts core research and development activities on behalf of the Company, is eligible to receive a 43.5% refundable tax incentive for qualified research and development activities. For the years ended December 31, 2018, 2017 and 2016, $1.6 million, $0.9 million and $0.3 million, respectively, were recorded as a reduction to research and development expenses in the consolidated statements of operations. These amounts represented 43.5% for 2018 and 2017 and 45% for 2016, of the Company's qualified research and development spending in Australia. The refund is denominated in Australian dollars and, therefore, the related receivable is re-measured into U.S. dollars as of each reporting date. For the years ended December 31, 2018, 2017 and 2016, the Company recorded in its consolidated statements of operations unrealized foreign currency exchange (losses) gains of $(0.2) million, $0.1 million, and less than $(0.1) million, respectively, related to this tax incentive receivable. As of December 31, 2018 and 2017, the Company's tax incentive receivable from the Australian government was $1.5 million and $0.9 million, respectively.

14. Restructuring

On July 19, 2016, the Company announced that following a comprehensive review of its assets and clinical programs, as well as feedback from regulatory authorities, the Company refocused its resources on development of a differentiated second-generation MetAP2 inhibitor, ZGN-1061. As part of the strategic restructuring, the Company reorganized its operations to align with its new priorities focused on ZGN-1061 development. The Company's workforce was reduced by approximately 31% as of December 2016.

During the year ended December 31, 2016, the Company recorded $1.4 million of restructuring-related costs in operating expenses, including employee severance, benefits and related costs, as well as a stock option modification. The stock option modification was a one-time, non-cash expense of $0.2 million and is included in the stock-based compensation expense line items of both the consolidated statements of cash flows and the consolidated statements of changes in stockholders' equity as of December 31, 2016. The Company does not expect to incur any additional significant costs associated with this restructuring.

The following table summarizes the restructuring costs by category for the periods indicated:

	Year Ended December 31, 2016		
	(in thousands)		
	Cash	Non-Cash	Total
Research and development	$ 455	$ 7	$ 462
General and administrative	768	173	941
	$ 1,223	$ 180	$ 1,403

The following table summarizes the restructuring reserve for the periods indicated:

	Year Ended December 31, 2017
	(in thousands)
Restructuring reserve beginning balance	$ 376
Restructuring expenses incurred during the period	24
Amounts paid during the period	(400)
Restructuring reserve ending balance	$ —

15. Quarterly Financial Data (Unaudited)

The following information has been derived from unaudited consolidated financial statements that, in the opinion of management, include all recurring adjustments necessary for a fair statement of such information.

	Three Months Ended			
	March 31, 2018	June 30, 2018	September 30, 2018	December 31, 2018
	(in thousands, except per share data)			
Revenue	$ —	$ —	$ —	$ —
Operating expenses	15,702	15,560	15,169	14,691
Net loss	(15,956)	(15,775)	(15,067)	(14,570)
Net loss per share, basic and diluted	$ (0.58)	$ (0.57)	$ (0.41)	$ (0.39)
Weighted average common shares outstanding, basic and diluted	27,541,594	27,565,064	36,619,575	37,036,065

	Three Months Ended			
	March 31, 2017	June 30, 2017	September 30, 2017	December 31, 2017
	(in thousands, except per share data)			
Revenue	$ —	$ —	$ —	$ —
Operating expenses	13,265	13,536	12,840	13,358
Net loss	(13,011)	(13,347)	(12,585)	(13,085)
Net loss per share, basic and diluted	$ (0.48)	$ (0.49)	$ (0.46)	$ (0.48)
Weighted average common shares outstanding, basic and diluted	27,350,673	27,407,408	27,483,550	27,489,397

16. Subsequent Events

On February 12, 2019, the Company entered into an operating lease with Shigo Center Plaza Owners, LLC, for approximately 17,705 square feet of office space for a new headquarters located at 1-3 Center Plaza, Boston, Massachusetts. The lease has a term of 124 months, and the Company has an option to extend this lease for 60 additional months. As part of the agreement the Company is required to maintain a letter of credit, which upon signing was $1.3 million. Under the agreement, the Company will pay a monthly rent starting four months after the Commencement Date as set forth below.

Lease Year:		Monthly Base Rent
1	$	82,623
2	$	84,099
3	$	85,574
4	$	87,050
5	$	88,525
6	$	90,000
7	$	91,476
8	$	92,951
9	$	94,427
10	$	95,902

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

Disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) are designed only to provide reasonable assurance that they will meet their objectives. Under the supervision and with the participation of our management, including our principal executive officer and principal financial officer, we conducted an evaluation of the effectiveness, as of December 31, 2018, of the design and operation of our disclosure controls and procedures, as such term is defined in Exchange Act Rules 13a-15(e) and 15d-15(e). Based on this evaluation, our principal executive officer and principal financial officer have concluded that, as of such date, our disclosure controls and procedures are effective to ensure that information required to be disclosed by us in our Exchange Act reports is recorded, processed, summarized, and reported within the time periods specified in the SEC's rules and forms, and that such information is accumulated and communicated to our management, including our principal executive officer and principal financial officer, as appropriate to allow timely decisions regarding required disclosure.

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 Rule 13a-15(f) under the Exchange Act. Our internal control system is designed to provide reasonable assurance to our management and board of directors regarding the preparation and fair presentation of published financial statements. All internal control systems, no matter how well designed, have inherent limitations. Therefore, even those systems determined to be effective can provide only reasonable assurance with respect to financial statement preparation and presentation.

Our management has assessed the effectiveness of our internal control over financial reporting as of December 31, 2018. In making this assessment, management used the criteria set forth by the Committee of Sponsoring Organizations of the Treadway Commission ("COSO") in its 2013 *Internal Control—Integrated Framework*. Based on this assessment, our management has concluded that as of December 31, 2018 our internal control over financial reporting is effective.

As an Emerging Growth Company, as defined under the terms of the Jobs Act of 2012, our independent registered accounting firm is not required to issue an attestation report on the internal control over financial reporting.

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) or 15d-15(d) under the Exchange Act) during the fourth quarter of the year ended December 31, 2018 that have materially affected, or are reasonably likely to materially affect, our internal control over financial reporting.

ITEM 9B. OTHER INFORMATION

None.

PART III

ITEM 10. DIRECTORS, EXECUTIVE OFFICERS AND CORPORATE GOVERNANCE

The information required under this item is incorporated herein by reference to the Company's definitive proxy statement pursuant to Regulation 14A, which proxy statement will be filed with the Securities and Exchange Commission not later than 120 days after the close of the Company's fiscal year ended December 31, 2018.

ITEM 11. EXECUTIVE COMPENSATION

The information required under this item is incorporated herein by reference to the Company's definitive proxy statement pursuant to Regulation 14A, which proxy statement will be filed with the Securities and Exchange Commission not later than 120 days after the close of the Company's fiscal year ended December 31, 2018.

ITEM 12. SECURITY OWNERSHIP OF CERTAIN BENEFICIAL OWNERS AND MANAGEMENT AND RELATED STOCKHOLDER MATTERS

The information required under this item is incorporated herein by reference to the Company's definitive proxy statement pursuant to Regulation 14A, which proxy statement will be filed with the Securities and Exchange Commission not later than 120 days after the close of the Company's fiscal year ended December 31, 2018.

ITEM 13. CERTAIN RELATIONSHIPS AND RELATED TRANSACTIONS, AND DIRECTOR INDEPENDENCE

The information required under this item is incorporated herein by reference to the Company's definitive proxy statement pursuant to Regulation 14A, which proxy statement will be filed with the Securities and Exchange Commission not later than 120 days after the close of the Company's fiscal year ended December 31, 2018.

ITEM 14. PRINCIPAL ACCOUNTING FEES AND SERVICES

The information required under this item is incorporated herein by reference to the Company's definitive proxy statement pursuant to Regulation 14A, which proxy statement will be filed with the Securities and Exchange Commission not later than 120 days after the close of the Company's fiscal year ended December 31, 2018.

PART IV

ITEM 15. EXHIBITS, FINANCIAL STATEMENT SCHEDULES

(a) 1. Consolidated Financial Statements.

For a list of the consolidated financial statements included herein, see Index on page 73 of this report.

2. Financial Statement Schedules.

All required information is included in the financial statements or notes thereto.

3. List of Exhibits.

See the Exhibit Index in Item 15(b) below.

(b) Exhibit Index.

Exhibit No.	Description
3.1	Ninth Amended and Restated Certificate of Incorporation of the Registrant, as currently in effect (incorporated by reference to Exhibit 3.1 of the Registrant's Form 8-K filed on June 24, 2014)
3.2	Amended and Restated By-laws of the Registrant, as currently in effect (incorporated by reference to Exhibit 3.2 of the Registrant's Form 8-K filed on June 24, 2014)
4.1	Specimen Common Stock Certificate (incorporated by reference to Exhibit 4.1 of the Registrant's Registration Statement on Form S-1 (File No. 333-195391) filed on June 18, 2014)
4.2	Third Amended and Restated Investors' Rights Agreement by and among the Registrant and certain of its stockholders dated November 25, 2013 (incorporated by reference to Exhibit 4.2 of the Registrant's Registration Statement on Form S-1 (File No. 333-195391) filed on June 18, 2014)
10.1#	Amended and Restated 2006 Stock Option Plan and forms of award agreements thereunder (incorporated by reference to Exhibit 10.1 of the Registrant's Registration Statement on Form S-1 (File No. 333-195391) filed on June 18, 2014)
10.2#	2014 Stock Option and Incentive Plan and forms of award agreements thereunder (incorporated by reference to Exhibit 10.2 of the Registrant's Registration Statement on Form S-1 (File No. 333-195391) filed on June 18, 2014)
10.3(a)†	Exclusive License Agreement by and between the Registrant and Chong Kun Dang Pharmaceutical Corp. of South Korea, dated July 6, 2009, as amended (incorporated by reference to Exhibit 10.3 of the Registrant's Registration Statement on Form S-1 (File No. 333-195391) filed on June 18, 2014)
10.3(b)	Amendment No. 4 to Exclusive License Agreement by and between the Registrant and Chong Kun Dang Pharmaceutical Corporation, dated October 29, 2014 (incorporated by reference to Exhibit 10.3(b) of the Registrant's Registration Statement on Form S-1 (File No. 333-201439) filed on January 12, 2015)
10.4	Subscription Agreement by and between the Registrant and Chong Kun Dang Pharmaceutical Corporation, dated November 20, 2014 (incorporated by reference to Exhibit 10.4 of the Registrant's Registration Statement on Form S-1 (File No. 333-201439) filed on January 12, 2015)
10.5	Letter by and between the Registrant and Thomas E. Hughes, dated July 25, 2008 (incorporated by reference to Exhibit 10.5 of the Registrant's Registration Statement on Form S-1 (File No. 333-195391) filed on June 18, 2014)
10.6	Employee Non-Competition, Non-Solicitation, Confidentiality and Assignment Agreement by and between the Registrant and Thomas E. Hughes, dated July 29, 2008 (incorporated by reference to Exhibit 10.6 of the Registrant's Registration Statement on Form S-1 (File No. 333-195391) filed on June 18, 2014)
10.7	Letter by and between the Registrant and Dennis D. Kim, dated August 23, 2011 (incorporated by reference to Exhibit 10.7 of the Registrant's Registration Statement on Form S-1 (File No. 333-195391) filed on June 18, 2014)

Exhibit No.	Description
10.8	Employee Non-Competition, Non-Solicitation, Confidentiality and Assignment Agreement by and between the Registrant and Dennis D. Kim, dated August 29, 2013 (incorporated by reference to Exhibit 10.8 of the Registrant's Registration Statement on Form S-1 (File No. 333-195391) filed on June 18, 2014)
10.9	Letter by and between the Registrant and Patricia L. Allen, dated December 10, 2012 (incorporated by reference to Exhibit 10.9 of the Registrant's Registration Statement on Form S-1 (File No. 333-195391) filed on June 18, 2014)
10.10	Employee Non-Competition, Non-Solicitation, Confidentiality and Assignment Agreement by and between the Registrant and Patricia L. Allen, dated August 29, 2013 (incorporated by reference to Exhibit 10.10 of the Registrant's Registration Statement on Form S-1 (File No. 333-195391) filed on June 18, 2014)
10.11(a)	Form of Indemnification Agreement, to be entered into between the Registrant and its directors (incorporated by reference to Exhibit 10.11(a) of the Registrant's Registration Statement on Form S-1 (File No. 333-195391) filed on June 18, 2014)
10.11(b)	Form of Indemnification Agreement, to be entered into between the Registrant and its officers (incorporated by reference to Exhibit 10.11(b) of the Registrant's Registration Statement on Form S-1 (File No. 333-195391) filed on June 18, 2014)
10.12#	Senior Executive Cash Incentive Bonus Plan (incorporated by reference to Exhibit 10.12 of the Registrant's Registration Statement on Form S-1 (File No. 333-195391) filed on June 18, 2014)
10.13†	Exclusive License Agreement by and between the Registrant and Children's Medical Center Corporation, dated January 4, 2007, as amended January 15, 2007 (incorporated by reference to Exhibit 10.13 of the Registrant's Registration Statement on Form S-1 (File No. 333-195391) filed on June 18, 2014)
10.14	Commercial Lease by and between the Registrant and Minerva Holdings, LLC, dated May 15, 2014 (incorporated by reference to Exhibit 10.14 of the Registrant's Registration Statement on Form S-1 (File No. 333-195391) filed on June 18, 2014)
10.15	Commercial Lease by and between the Company and Contour LLC, dated March 30, 2015 (incorporated by reference to Exhibit 10.1 of the Registrant's Quarterly Report on Form 10-Q (File No. 001-36510) filed on May 14, 2015)
10.16#	2014 Employee Stock Purchase Plan (incorporated by reference to Exhibit 10.15 of the Registrant's Registration Statement on Form S-1 (File No. 333-195391) filed on June 18, 2014)
10.17	Severance and Change in Control Agreement by and between the Registrant and Thomas E. Hughes, PhD. dated as of June 30, 2016 (incorporated by reference to Exhibit 10.1 of the Registrant's Quarterly Report on Form 10-Q (File No. 001-36510) filed on August 5, 2016)
10.18	Severance and Change in Control Agreement by and between the Registrant and Patricia Allen dated as of June 30, 2016 (incorporated by reference to Exhibit 10.4 of the Registrant's Quarterly Report on Form 10-Q (File No. 001-36510) filed on August 5, 2016)
10.19	Severance and Change in Control Agreement by and between the Registrant and Dennis Kim, M.D., M.B.A. dated as of June 30, 2016 (incorporated by reference to Exhibit 10.5 of the Registrant's Quarterly Report on Form 10-Q (File No. 001-36510) filed on August 5, 2016)
10.20	Loan and Security Agreement between the Registrant, as borrower, and Silicon Valley Bank, as lender dated December 29, 2017 (incorporated by reference to Exhibit 10.1 of the Registrant's Form 8-K (File No. 001-36510) filed January 5, 2018)
10.21	Employment Offer Letter Agreement by and between the Registrant and Jeffrey S. Hatfield, effective as of October 9, 2017 (incorporated by reference to Exhibit 10.2 of the Registrant's Form 8-K (File No. 001-36510) filed on October 12, 2017)
10.22	Severance and Change in Control Agreement by and between Registrant and Jeffrey S. Hatfield, effective as of October 9, 2017 (incorporated by reference to Exhibit 10.3 of the Registrant's Form 8-K (File No. 001-36510) filed on October 12, 2017)

Exhibit No.	Description
10.23#	Non-Qualified Stock Option Agreement Inducement Award by and between Registrant and Jeffrey S. Hatfield granted on October 9, 2017 (incorporated by reference to Exhibit 10.23 of the Registrant's Annual Report on Form 10-K (File No. 001-36510) filed on March 3, 2018)
10.24#	Non-Qualified Stock Option Agreement Inducement Award by and between Registrant and Jeffrey S. Hatfield granted on October 9, 2017 (incorporated by reference to Exhibit 10.24 of the Registrant's Annual Report on Form 10-K (File No. 001-36510) filed on March 3, 2018)
10.25	Waiver to Financing Condition by and between Registrant and Jeffrey S. Hatfield, effective as of December 29, 2017 (incorporated by reference to Exhibit 10.25 of the Registrant's Annual Report on Form 10-K (File No. 001-36510) filed on March 3, 2018)
10.26	Employment Offer Letter Agreement by and between the Registrant and Brian P. McVeigh, effective as of May 29, 2018 (incorporated by reference to Exhibit 10.1 of the Registrant's Form 8-K (File No. 001-36510) filed May 30, 2018)
10.27	Severance and Change in Control Agreement by and between Zafgen, Inc. and Brian P. McVeigh, effective as of May 29, 2018 (incorporated by reference to Exhibit 10.2 of the Registrant's Form 8-K (File No. 001-36510) filed May 30, 2018)
10.28	Non-Qualified Stock Option Agreement Inducement Award by and between Registrant and Brian P. McVeigh granted on May 29, 2018 (incorporated by reference to Exhibit 10.3 of the Registrant's Form 10-Q (File No. 001-36510) filed August 9, 2018)
16.1	Letter of Edelstein and Company LLP (incorporated by reference to Exhibit 16.1 of the Registrant's Registration Statement on Form S-1 (File No. 333-201439) filed on January 12, 2015)
21.1	Subsidiaries of the Registrant (incorporated by reference to Exhibit 21.1 of the Registrant's Registration Statement on Form S-1 (File No. 333-195391) filed on June 18, 2014)
23.1*	Consent of PricewaterhouseCoopers LLP, independent registered public accounting firm
31.1*	Certification of Principal Executive Officer pursuant to Rule 13a-14(a) or Rule 15d-14(a) of the Securities Exchange Act of 1934, as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002.
31.2*	Certification of Principal Financial Officer pursuant to Rule 13a-14(a) or Rule 15d-14(a) of the Securities Exchange Act of 1934, as adopted pursuant to Section 302 of the Sarbanes-Oxley Act of 2002
32.1**	Certification of Principal Executive Officer and Principal Financial Officer pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002
101*	Interactive Data Files regarding (a) our Consolidated Balance Sheets as of December 31, 2018 and 2017, (b) our Consolidated Statements of Operations and Comprehensive Loss for the Years Ended December 31, 2018, 2017 and 2016, (c) our Consolidated Statements of Changes in Stockholders' Equity, (d) our Consolidated Statements of Cash Flows for the Years Ended December 31, 2018, 2017 and 2016 and (e) the Notes to such Consolidated Financial Statements

* Filed herewith.
** Furnished herewith.
† Application has been made to the Securities and Exchange Commission for confidential treatment of certain provisions. Omitted material for which confidential treatment has been requested has been filed separately with the Securities and Exchange Commission.
# Represents management compensation plan.

ITEM 16. FORM 10-K SUMMARY

None.

SIGNATURES

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

ZAFGEN, INC.

Date: March 14, 2019

By: /s/ Jeffrey Hatfield
Jeffrey Hatfield
Chief Executive Officer
(Principal Executive Officer)

Date: March 14, 2019

By: /s/ Patricia L. Allen
Patricia L. Allen
Chief Financial Officer
(Principal Financial and Accounting Officer)

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

Name	Title	Date
/s/ Jeffrey Hatfield Jeffrey Hatfield	Chief Executive Officer and Director *(Principal Executive Officer)*	March 14, 2019
/s/ Patricia L. Allen Patricia L. Allen	Chief Financial Officer *(Principal Financial and Accounting Officer)*	March 14, 2019
/s/ Peter Barrett, Ph.D. Peter Barrett, Ph.D.	Chairman of the Board of Directors	March 14, 2019
/s/ Thomas O. Daniel, M.D. Thomas O. Daniel, M.D.	Director	March 14, 2019
/s/ Wendy Everett Wendy Everett Sc.D.	Director	March 14, 2019
/s/ John L. LaMattina, Ph.D. John L. LaMattina, Ph.D.	Director	March 14, 2019
/s/ Cameron Geoffrey McDonough, M.D. Cameron Geoffrey McDonough, M.D.	Director	March 14, 2019
/s/ Robert J. Perez Robert J. Perez	Director	March 14, 2019
/s/ Frank E. Thomas Frank E. Thomas	Director	March 14, 2019

Exhibit 23.1

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We hereby consent to the incorporation by reference in the Registration Statements on Form S-3 (No. 333-219834 and 333-228328) and Form S-8 (Nos. 333-210216, 333-196900, 333-204931, 333-216602, 333-223561 and 333-228326) of Zafgen, Inc. of our report dated March 14, 2019 relating to the financial statements, which appears in this Form 10-K.

/s/ PricewaterhouseCoopers LLP
Boston, Massachusetts
March 14, 2019

Exhibit 31.1

Certification

I, Jeffrey Hatfield, certify that:

1. I have reviewed this Annual Report on Form 10-K for the year ended December 31, 2018 of Zafgen, Inc.;

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

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

4. The registrant's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) 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(s) 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, 2019

/s/ Jeffrey Hatfield

Jeffrey Hatfield
Chief Executive Officer
(Principal Executive Officer)

Exhibit 31.2

Certification

I, Patricia Allen, certify that:

1. I have reviewed this Annual Report on Form 10-K for the year ended December 31, 2018 of Zafgen, Inc.;

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

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

4. The registrant's other certifying officer(s) and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) 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(s) 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, 2019

/s/ Patricia Allen

Patricia Allen
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 on Form 10-K of Zafgen, Inc. (the "Company") for the period ended December 31, 2018, as filed with the Securities and Exchange Commission on the date hereof (the "Report"), each of the undersigned officers hereby certify, pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, 18 U.S.C. Section 1350, that to his or her knowledge:

1) the Report which this statement accompanies fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934, as amended; and

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

Dated: March 14, 2019

/s/ Jeffrey Hatfield
Jeffrey Hatfield
Chief Executive Officer
(Principal Executive Officer)

Dated: March 14, 2019

/s/ Patricia Allen
Patricia Allen
Chief Financial Officer
(Principal Financial and Accounting Officer)