ZAFGEN, INC.

FORM 10-K
(Annual Report)

Filed 03/25/15 for the Period Ending 12/31/14

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SIC Code	2834 - Pharmaceutical Preparations
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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, 2014

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	**27-3857670**
(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 and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post 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 or a smaller reporting company. See definitions of "large accelerated filer," "accelerated filer" and "smaller reporting company" in 12b-2 of the Exchange Act.

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

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 30, 2014 (based on the last reported sale price on the Nasdaq Global Market as of such date) was $150.3 million. As of March 17, 2015 there were 26,856,329 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, 2014. Portions of such definitive proxy statement are incorporated by reference into Part III of this Annual Report on Form 10-K.

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ZAFGEN, INC.

ANNUAL REPORT ON FORM 10-K

For the Year Ended December 31, 2014

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PART I

This Annual Report on Form 10-K, or this Annual Report, contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended, and are subject to the "safe harbor" created by those sections. Any statements about our expectations, beliefs, plans, objectives, assumptions or future events or performance are not historical facts and may be forward-looking. Some of the forward-looking statements can be identified by the use of forward-looking terms such as "believes," "expects," "may," "will," "should," "seek," "intends," "plans," "estimates," "projects," "anticipates," or other comparable terms. These forward-looking statements involve risk and uncertainties. We cannot guarantee future results, levels of activity, performance or achievements, and you should not place undue reliance on our forward-looking statements. Our actual results may differ significantly from the results discussed in the forward-looking statements. Factors that might cause such a difference include, but are not limited to, those set forth in "Item 1A. Risk Factors" and elsewhere on Form 10-K, or Annual Report. Except as may be required by law, we have no plans to update our forward-looking statements to reflect events or circumstances after the date of this Annual Report. We caution readers not to place undue reliance upon any such forward-looking statements, which speak only as of the date made.

Unless the content requires otherwise, references to "Zafgen," "ZFGN," "the Company," "we," "our," and "us," in this Annual Report refer to Zafgen, Inc. and our subsidiaries.

ITEM 1. BUSINESS

Overview

We are a biopharmaceutical company dedicated to significantly improving the health and well-being of patients affected by obesity and complex metabolic disorders. Beloranib, our lead product candidate, is a novel, first-in-class, twice-weekly subcutaneous, or SC, injection being developed for the treatment of multiple indications, including severe obesity in two rare diseases, Prader-Willi syndrome, or PWS, and hypothalamic injury-associated obesity, or HIAO, including craniopharyngioma-associated obesity; and severe obesity in the general population.

Obesity is a complex medical disorder involving appetite dysregulation and altered lipid and energy metabolism that results in excessive accumulation of fat tissue. Weight loss and hunger control are urgently needed for certain subpopulations of obese patients, in which obesity is life-threatening and a co-morbidity of an underlying condition such as PWS and HIAO that, while rare, occurs most commonly as a consequence of treatment for craniopharyngioma and other mid-brain tumors. PWS and HIAO are characterized by uncontrollable hunger resulting from damage to or impaired functioning of the hypothalamus, an area of the brain responsible for many functions including the neurophysiological drive to eat.

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. In January 2014, we completed a Phase 2a clinical trial evaluating beloranib's ability to reduce body weight and to improve hyperphagia in patients with PWS. In this trial, we observed reductions in body weight, body mass and body fat content and reductions in hyperphagia-related behaviors. Based on the results of this Phase 2a trial, we initiated our Phase 3 clinical program, which is planned to consist of two Phase 3 clinical trials of beloranib in patients with PWS, with the first Phase 3 trial in the United States having started in September 2014. We expect to report six month data from this U.S. clinical trial by early second quarter of 2016. We plan to initiate our second Phase 3 clinical trial of beloranib in patients with PWS in the European Union in the middle of 2015. Beloranib received orphan designation for the treatment of PWS by both the U.S. Food and Drug Administration, or FDA, and the European Commission in January 2013 and July 2014, respectively. We believe that rare conditions such as PWS afford us an opportunity to rapidly develop and commercialize beloranib using smaller, more focused and less costly clinical trials, relative to those required to develop beloranib for the broader severe obesity population.

Published population studies estimate that the prevalence of PWS in the United States and in the European Union 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 our 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 benefit 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. Since beloranib works through a novel mechanism that does not appear to require a fully functioning hypothalamic control pathway, we believe that obese patients with conditions in which increased hunger is central to the disease may respond well to treatment with beloranib.

Zafgen was founded in 2005 to explore novel approaches to obesity therapeutics, including agents known to inhibit methionine aminopeptidase 2, or MetAP2, that had been found to drive unprecedented weight loss and metabolic improvements in mice. After performing a wide range of experiments to validate the effects of MetAP2 inhibitors in validated animal models, we committed the full resources of the company to testing the efficacy and safety of MetAP2 inhibition in obese patients and to establishing the feasibility of MetAP2 inhibitors for eventual commercialization. This effort led to our initiation of medicinal chemistry efforts to identify novel MetAP2 inhibitors, and to search for compounds that were more advanced in clinical development. We identified beloranib as a suitable in-licensing candidate, and, in parallel with preparing beloranib for use in otherwise healthy but obese patients, we conducted our own chemistry program to identify compounds with complementary characteristics. After completing studies to establish preliminary safety, mechanism of action, manufacturing feasibility and clinical proof of concept, we advanced beloranib as a clinical development candidate and explored its application in severely obese patient populations. Our early clinical experience highlighted several key aspects of beloranib's actions, including rapid and robust weight loss, changes in circulating hormones known to impact fat metabolism, clinically significant reductions in cardiovascular disease risk markers and a particularly striking impact on hunger. These benefits may be of particular relevance to patients suffering from severe obesity and life-limiting obesity driven by other underlying conditions, and for whom existing therapies fail to bring needed benefits.

HIAO is most commonly caused by damage incurred during removal of a central nervous system tumor called craniopharyngioma, but it can also result from less common types of hypothalamic injury such as strokes, brain trauma, or radiation therapy to the brain. We recently completed a Phase 2 clinical trial of beloranib administered twice weekly in 14 patients with HIAO caused by the treatment of craniopharyngioma or pituitary macroadenoma. We observed mean weight loss of 3.4 kg and 6.2 kg in patients with HIAO after four and eight weeks of treatment with beloranib, respectively, in contrast to 0.3 kg mean weight loss in patients treated with placebo for four weeks. Improvements in cardiovascular disease risk factors of lipids and inflammation (measured by C-reactive protein) were also observed. In 2015, we plan to establish the regulatory path for a registration program with U.S. and European Union regulatory authorities for our HIAO program, and will decide whether to pursue additional clinical trials of beloranib in patients with HIAO following completion of our Phase 3 trial in the United States of beloranib in patients with PWS. We plan to seek orphan drug designation for the treatment of craniopharyngioma-associated obesity in the United States and European Union.

We are pursuing clinical development of beloranib as a treatment for severely obese patients in the general population, including patients otherwise eligible for bariatric surgery. Bariatric surgery eligibility criteria generally identify surgical candidates as those patients with body mass indices, or BMIs, greater than 40 kg/m^2, or those with BMIs over 35 kg/m^2 who also have a significant and uncontrolled co-morbid condition. Based on these criteria, it is estimated conservatively that there will be at least 16 million adults in the United States eligible for bariatric surgery by the time beloranib or another MetAP2 inhibitor could become available

commercially. Bariatric surgery results in significant weight loss, but the financial expense and the potential for complications, adverse events and longer-term side effects limit its overall adoption, with only a few hundred thousand patients in the United States undergoing bariatric surgery each year. Existing pharmacotherapies result in less weight loss than surgical options, and these therapies not only have undesirable side effects, but also have risk of abuse. Due to the significant barriers associated with bariatric surgery and the limited weight loss potential of currently marketed pharmaceutical products, there is a significant unmet need for the treatment of patients with severe obesity. We believe this patient population would benefit from MetAP2 inhibitor treatment through the reduction of body weight and through improvement of other co-morbid conditions.

In 2013, we completed a 12-week Phase 2a clinical trial of beloranib administered twice weekly in obese patients. We observed placebo-adjusted weight loss of up to 10.3% after 12 weeks of treatment with beloranib. In addition, we observed reductions in levels of low density lipoprotein cholesterol, C-reactive protein and systolic blood pressure. Patients treated with beloranib also reported reduced hunger, as assessed using a visual analog scale, a widely used self-reported measure of hunger and related endpoints. We initiated a Phase 2b clinical trial of beloranib as a treatment for severe obesity in the general population in patients who also have type 2 diabetes in December 2014. We expect to report interim six month data from this clinical trial in late 2015 or early 2016. We are also evaluating additional proprietary MetAP2 inhibitors beyond beloranib as potential development candidates that would provide increased patient convenience in the form of oral dosing, or an otherwise improved clinical profile. A decision on whether to subsequently advance beloranib into pivotal trials for severe obesity or to leverage the opportunity to advance another MetAP2 inhibitor into early development for severe obesity is anticipated to be made on the basis of results obtained from our Phase 3 clinical trial of beloranib in patients with PWS and discussions with regulatory authorities. MetAP2 inhibitors may also have utility in the treatment of other metabolic diseases, such as nonalcoholic fatty liver disease, or NAFLD, and nonalcoholic steatohepatitis, or NASH. In a mouse model of diabetes, NAFLD, and NASH, our second product candidate, ZGN-839, a MetAP2 inhibitor, reduced the severity of NAFLD and NASH.

Beloranib is a novel, first-in-class injectable small molecule therapy with a unique mechanism of action that reduces hunger while stimulating the use of stored fat as an energy source. Beloranib is the first anti-obesity agent with the potential to address two important abnormalities that are present in the obese patient—hunger that is inappropriate relative to the amount of energy stored as fat and dysregulation of fat metabolism, which causes more fat to be made and stored in an obese patient than in a lean person. Beloranib 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 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 packages 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.

We have completed six clinical trials, including three Phase 2 clinical trials, evaluating beloranib in over 200 patients. Although these clinical trials were of short duration and designed to demonstrate safety and tolerability, significant decreases in both body weight and sense of hunger were observed in patients treated with beloranib when compared to the placebo group. In addition, we observed improvements in cardiovascular disease risk factors such as plasma total cholesterol, low density lipoprotein cholesterol and C-reactive protein. Additional clinical trials of longer-term treatment with beloranib designed to demonstrate efficacy are required before we can submit an NDA for beloranib as a treatment for any indication that we are pursuing. In our ongoing Phase 2b clinical trial of beloranib as a treatment for severe obesity in the general population and our ongoing Phase 3 clinical program of beloranib as a treatment for obesity and hyperphagia patients with PWS, patients are being treated with beloranib for a substantially longer period of time than as treated in our earlier clinical trials. Across our completed clinical trials, beloranib has been well-tolerated at doses in the range of 1.0 mg to 2.0 mg administered twice weekly, and has not been associated with serious side effects. Laboratory safety measures, vital signs and electrocardiograms have been unremarkable in all completed clinical trials for all doses of beloranib tested.

Product Pipeline

The following table summarizes our product pipeline and development status of our product candidates for the treatment of indications we are currently pursuing:

Indication	Product Candidate	Stage of Development	Development Status
Obesity and hyperphagia in patients with PWS	Beloranib	Phase 3	• Phase 2a clinical trial completed • Phase 3 clinical trial of beloranib in patients with PWS began in the United States in September 2014, with six month data anticipated by early second quarter of 2016 • Phase 3 clinical trial of beloranib in patients with PWS in the European Union expected to begin in the middle of 2015
HIAO	Beloranib	Phase 2	• Phase 2 clinical trial recently completed
Severe obesity in the general population	Beloranib	Phase 2b	• Phase 2a clinical trial completed • Phase 2b clinical trial began in December 2014 with interim six month data anticipated in late 2015 or early 2016 • Advancement into pivotal trials under consideration
	Second-generation MetAP2 inhibitors	Pre-clinical	• Development candidates under consideration
NAFLD, NASH and abdominal obesity	ZGN-839	Pre-clinical	• Pre-clinical studies ongoing • Investigational New Drug Application, or IND, filing anticipated by the middle of 2015

Populations of Interest

Obesity Caused by Rare Conditions

Obesity is a complex medical disorder involving appetite dysregulation and altered lipid and energy metabolism that results in excessive accumulation of fat tissue. We initially plan to develop beloranib for the treatment of subpopulations of obese patients, including those with rare conditions such as PWS and HIAO, where obesity is a co-morbidity of an underlying condition. These conditions frequently are characterized by

increased and life-threatening hunger that occurs secondary to damage to the hypothalamus, genetic conditions affecting embryological development or function of the hypothalamus, or conditions that occur as a result of certain drug side effects, radiation therapy, or other impairments to the normal function of the hypothalamus. Regardless of the causative agent or condition, the resultant damage to the hypothalamus impairs its normal function, including the ability to modulate hunger. These conditions are most often associated with a severe and life-limiting form of obesity and neither dietary interventions nor currently available pharmaceutical therapies bring meaningful benefit to these patients, for whom bariatric surgery is generally contra-indicated. Based on results from animal experiments in which compromised hypothalamic function caused hunger and obesity, we believe that beloranib may have utility in the treatment of severe obesity and hyperphagia, or insatiable life-threatening hunger and hunger-related behavior, in human disease settings in which hypothalamic food intake control centers are compromised. We are developing beloranib in these subpopulations of patients as a treatment for obesity and hyperphagia in patients with PWS and HIAO, and are continuing to explore the use of beloranib as a treatment for severe obesity in the general population.

PWS

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 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 as well as 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 patient with PWS's ability to live independently, requiring costly and constant supervision to prevent overeating. Without supervision, patients with PWS are likely to die prematurely as a result of choking, stomach rupture or tissue necrosis, or from complications caused by morbid obesity, such as right heart failure and respiratory failure. 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 are cared for in their homes and their families undertake substantial effort to create physical barriers to eating. These efforts result in extremely stressful environments as caregivers often place locks and alarms on cabinets and refrigerators that contain food to impede a patient with PWS'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 European Union 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, and we believe that, due to the severity of the condition and its unique attributes, the vast majority of patients affected by PWS are diagnosed. We believe that approximately 40-50% of patients with PWS are 12 years of age or older. We believe that further information regarding the prevalence of PWS will become available through a patient registry that is currently being developed by the Foundation for Prader-Willi Research.

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. Furthermore, bariatric 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. In January 2014, we completed a Phase 2a clinical trial evaluating beloranib's ability to reduce body weight and to improve hyperphagia in patients with PWS. In this clinical trial, we observed reductions in body weight, body mass, body fat content and hyperphagia-related behaviors in patients with PWS treated with beloranib. Based on the results of this Phase 2a trial, we initiated our Phase 3 clinical program, which is planned to consist of two Phase 3 clinical trials, of beloranib in patients with PWS, with the first Phase 3 trial in the United States having started in September 2014. We expect to report six month data from this U.S. clinical trial by early second quarter of 2016. We plan to initiate our second Phase 3 clinical trial of beloranib in patients with PWS in the European Union in the middle of 2015.

In January 2013 and July 2014, the FDA and European Commission, respectively, granted orphan designation for our application to treat PWS with beloranib. Orphan drug designation provides for seven years of marketing exclusivity in the United States and ten years of marketing exclusivity in the European Union.

HIAO

HIAO is most commonly caused by damage incurred during removal of a central nervous system tumor called craniopharyngioma, but it can also result from less common types of hypothalamic injury such as strokes, brain trauma, or radiation therapy to the brain. Approximately 30% to 50% of cases of craniopharyngioma are diagnosed in childhood and adolescence. Manifestations of craniopharyngioma include visual disturbances, headaches and impairment to the hypothalamus-pituitary axis affecting hormone secretion. Treatment of these tumors commonly involves radical surgical removal of the tumor mass by endoscopy or craniotomy, followed by radiation treatment, which results in disruption or removal of neighboring structures including the hypothalamus. Depending on the degree of damage to the hypothalamus caused by tumor removal and subsequent radiation, there may be greater variation in hyperphagia and obesity prevalence in patients with craniopharyngioma than patients with PWS. Post-treatment hypothalamic dysfunction results in hyperphagia in approximately 50% of these patients, resulting in obesity and a worsened quality of life.

Craniopharyngioma is a rare form of benign brain tumor that occurs most commonly during childhood and infiltrates near the optic nerve, pituitary gland and the hypothalamus. Published population studies estimate that the incidence of craniopharyngioma is 0.13 to 0.17 per 100,000 per year, or approximately 400 to 500 cases per year in the United States and 650 to 850 cases per year in the European Union. We believe patients with craniopharyngioma-associated obesity have a longer life expectancy than patients with PWS, which contributes to an increased risk of developing obesity-related co-morbid conditions such as type 2 diabetes in such patients.

Currently available therapeutic agents fail to provide satisfactory management of weight or hyperphagia in patients with HIAO, and bariatric surgery is not frequently employed in this patient population. We believe this is related to perceived risks of surgical interventions in this population including increased risk of post-surgical complications and minimal impact on the underlying problems of low metabolic rate and hyperphagia.

We recently completed a Phase 2 clinical trial of beloranib administered twice weekly in 14 patients with HIAO caused by the treatment of craniopharyngioma or pituitary macroadenoma. We observed mean weight loss of 3.4 kg and 6.2 kg in patients with HIAO after four and eight weeks of treatment with beloranib, respectively, in contrast to 0.3 kg mean weight loss in patients treated with placebo for four weeks. Improvements in cardiovascular disease risk factors of lipids and inflammation (as measured by C-reactive protein) were also

observed. In 2015, we plan to establish the regulatory path for a registration program with U.S. and European Union regulatory authorities for our HIAO program, and will decide whether to pursue additional clinical trials of beloranib in patients with HIAO following completion of our Phase 3 clinical trial in the United States of beloranib in patients with PWS. We plan to seek orphan drug designation for the treatment of craniopharyngioma-associated obesity in the United States and European Union.

Severe Obesity in the General Population

Our long-term intention is to pursue clinical development of beloranib or another MetAP2 inhibitor as a treatment for severely obese patients in the general population. We believe this patient population would benefit from MetAP2 inhibitor treatment through the reduction of body weight and through improvement of severity or symptoms of other co-morbid conditions. We believe that MetAP2 inhibitors have the potential to offer this patient population, most of which is not adequately responsive to available therapies, substantial health and quality of life benefits.

The most effective current treatment for severe obesity is bariatric surgery, including procedures such as the Roux-en-Y gastric bypass, adjustable gastric banding, sleeve gastrectomy and biliopancreatic diversion. Bariatric surgery produces dramatic and sustained weight loss, ranging on average from 20% to 35% one year post-procedure and reduces overall mortality, but it can result in numerous complications and adverse events including thrombotic events, such as pulmonary embolism, infection, internal bleeding, pulmonary disease and gastrointestinal obstruction, which sometimes require reoperation during the post-operative period. Longer-term side effects of bariatric surgery, such as poor nutrient absorption, strictures and hernias, have also been observed.

Bariatric surgery eligibility criteria generally identify surgical candidates as those patients with BMIs, greater than 40 kg/m^2, or those with BMIs over 35 kg/m^2 who also have a significant and uncontrolled co-morbid condition. Based on these criteria, it is estimated conservatively that there will be at least 16 million adults in the United States eligible for bariatric surgery by the time beloranib or another MetAP2 inhibitor could become available commercially. In addition to the BMI and co-morbidity eligibility criteria, patients need to satisfy a number of other criteria in order to have bariatric surgery; a severely obese patient must not have any known endocrine causes of obesity, a drug or alcohol problem, or an uncontrolled psychological condition, and must understand and appreciate the risks of the surgical intervention. According to the American Society for Metabolic & Bariatric Surgery and to HealthGrades, the average cost of bariatric surgery in the United States is approximately $22,000-$38,000. As a result of these limiting criteria and the financial commitments required, only a few hundred thousand patients undergo bariatric surgery each year even though over 16 million patients in the United States are eligible for the surgery based on BMI alone.

The pharmaceutical industry has undertaken several waves of activity to discover and develop new drugs for the treatment of obesity. Relative to bariatric surgery, pharmaceutical treatments have produced modest efficacy. In addition, existing pharmacotherapeutics for obesity often have undesirable adverse event profiles.

The following table summarizes information from pivotal trials supporting registration for the current pharmacological treatments for severe obesity and the key limitations of these treatments, and unless specified otherwise in the table below, weight loss data is based on one year or longer treatment with the drug:

Treatment	% Placebo-Adjusted Weight Loss*	Key Limitations**
Phentermine	Variable	• Short-term (a few weeks) use only • Should not be taken during pregnancy
Xenical ® /alli	3%	• Unpleasant gastrointestinal side effects related to dietary fat malabsorption • Should not be taken during pregnancy
Qsymia ®	6.6% at target dose of 7.5mg/46 mg 8.6-9.4% at high dose of 15mg/92mg	• Known human teratogen – cannot be used in women unless contraception can be assured
Belviq ®	3.1-3.3%	• Should not be taken during pregnancy or by women who are planning to become pregnant
Contrave	2.0-4.1%	• Patients should be monitored for suicidal thoughts and behaviors (black box warning, antidepressant class labeling) • Should not be taken during pregnancy
Saxenda ®	3.7-4.5%	• Should not be used in patients with a personal or family history of medullary thyroid carcinoma or in patients with multiple endocrine neoplasia syndrome type 2 (black box warning) • Should not be taken during pregnancy

* Placebo-adjusted weight loss refers to the difference in mean weight loss observed in drug-treated patients and the weight change within the same trial observed in placebo-treated patients. This analysis takes into account, at least in part, the impact of diet and lifestyle interventions employed in drug registration trials.

** Some patients in our clinical trials of beloranib have reported gastrointestinal side effects, such as nausea, diarrhea or vomiting as well as sleep disturbance. In addition, beloranib will likely carry a Category X label and therefore be contraindicated in pregnant women or women looking to become pregnant.

In 2013, we completed a 12-week Phase 2a clinical trial of beloranib administered twice weekly in obese patients. We observed placebo-adjusted weight loss, or weight loss observed beyond that seen in the control arm, of up to 10.3% after 12 weeks of treatment with beloranib. In addition, we observed reductions in levels of low density lipoprotein cholesterol, C-reactive protein and systolic blood pressure. Patients treated with beloranib also reported reduced hunger, as assessed using a visual analog scale, a widely used self-reported measure of hunger and related endpoints. We initiated a Phase 2b clinical trial of beloranib as a treatment for severe obesity in the general population in patients who also have type 2 diabetes in December 2014. We expect to report interim six month data from this clinical trial in late 2015 or early 2016. We are also evaluating additional proprietary MetAP2 inhibitors beyond beloranib as potential development candidates that would provide increased patient convenience in the form of oral dosing, or an otherwise improved clinical profile. A decision on whether to subsequently advance beloranib into pivotal trials for severe obesity or to leverage the opportunity to advance another MetAP2 inhibitor into early development for severe obesity is anticipated to be made on the basis of results obtained from our Phase 3 clinical program of beloranib in patients with PWS and discussions with regulatory authorities. Future clinical development may address the impact of beloranib or a related drug on type 2 diabetes and other common co-morbid conditions associated with obesity.

Our Strategy

Our objective is to be a leader in the discovery, development and commercialization of novel therapies to significantly improve the health and well-being of patients affected by obesity and complex metabolic disorders. Key elements of our strategy include:

- ***Advance the clinical development of beloranib in subpopulations of obese patients, including those with rare conditions, where obesity is a co-morbidity of an underlying condition.*** Diseases in this category include PWS, HIAO and monogenic loss of function mutations, including leptin deficiency and melanocortin receptor subclass 4 mutations. We believe that rare conditions such as PWS and HIAO afford us an opportunity to rapidly develop and commercialize beloranib using smaller, more focused and less costly clinical trials, relative to those required to develop beloranib for the broader severe obesity population. Beloranib exerts its weight loss effects using a novel mechanism that does not appear to require fully functioning hypothalamic control pathways. We believe this mechanism is well-suited for patients with obesity that is caused by the failure of hypothalamic food intake control mechanisms, in particular the control of insatiable life-threatening hunger and hunger-related behavior, or hyperphagia. In January 2014, we completed a Phase 2a clinical trial of beloranib as a treatment for obesity and hyperphagia in patients with PWS, the most common known genetic cause of life-threatening obesity. In this clinical trial, we observed reductions in body weight, body mass, body fat content and hyperphagia-related behaviors in patients with PWS treated with beloranib. Based on the results of this Phase 2a trial, we initiated our Phase 3 clinical program, which is planned to consist of two Phase 3 clinical trials of beloranib in patients with PWS, with the first Phase 3 trial in the United States having started in September 2014. We expect to report six month data from this U.S. clinical trial by early second quarter of 2016. We plan to initiate our second Phase 3 clinical trial of beloranib in patients with PWS in the European Union in the middle of 2015. We recently completed a Phase 2 clinical trial of beloranib administered twice weekly in 14 patients with HIAO caused by the treatment of craniopharyngioma or pituitary macroadenoma. We observed mean weight loss of 3.4 kg and 6.2 kg in patients with HIAO after four and eight weeks of treatment with beloranib, respectively, in contrast to 0.3 kg mean weight loss in patients treated with placebo for four weeks. In 2015, we plan to establish the regulatory path for a registration program with U.S. and European Union regulatory authorities for our HIAO program, and will decide whether to pursue additional clinical trials of beloranib in patients with HIAO following completion of our Phase 3 clinical trial in the United States of beloranib in patients with PWS.
- ***Advance the clinical development of MetAP2 inhibitors for the treatment of severely obese patients in the general population, including those who are candidates for bariatric surgery.*** We believe the severely obese patient population would benefit from MetAP2 inhibitor treatment through the reduction of body weight and through improvement of other co-morbid conditions. Bariatric surgery results in significant weight loss, but the financial expense and the potential for complications, adverse events and longer-term side effects limit its overall adoption, with only a few hundred thousand patients in the United States undergoing bariatric surgery each year. Existing pharmacotherapies result in less weight loss than surgical options, and these therapies not only have undesirable side effects, but also have risk of abuse. We completed a 12-week Phase 2a clinical trial of beloranib administered twice weekly in obese patients. We observed placebo-adjusted weight loss of up 10.3% after 12 weeks of treatment with beloranib in addition to reductions in levels of low density lipoprotein cholesterol, C-reactive protein and systolic blood pressure. We initiated a Phase 2b clinical trial of beloranib as a treatment for severe obesity in the general population in patients who also have type 2 diabetes in December 2014. We expect to report interim six month data from this clinical trial in late 2015 or early 2016. A decision on whether to subsequently advance beloranib into pivotal trials for severe obesity or to leverage the opportunity to advance another MetAP2 inhibitor into early development for severe obesity is anticipated to be made on the basis of results obtained from our Phase 3 clinical trial in the United States of beloranib in patients with PWS and discussions with regulatory authorities.
- ***Leverage the knowledge of our experienced team of drug developers that have deep expertise in the field of obesity, the function of MetAP2 inhibitors and metabolic diseases.*** Our management team has

deep expertise in obesity and related metabolic diseases, the function of MetAP2 inhibitors, the strengths and weaknesses of current treatments for obesity and the ability to recognize the potential of novel therapies for the treatment of obesity. Our team is complemented by highly experienced external consultants and collaborators in the areas of drug discovery, development and regulatory approval.

- ***Maintain flexibility in commercializing and maximizing the value of our development programs.*** While we intend to develop and commercialize beloranib for indications such as PWS and other rare conditions causing obesity, we may enter into strategic relationships with biotechnology or pharmaceutical companies to realize the full value of beloranib or our other earlier-stage development programs. For beloranib, we may enter into one or more strategic relationships to access broader geographic markets or additional indications. These relationships could focus on specific patient populations and their caregivers, on regional development, or on distribution and sales of beloranib.
- ***Development of other potential product candidates.*** We have a second program focused on the delivery of MetAP2 inhibitors with targeted tissue distribution that shows early promise in animal models of NAFLD, NASH and abdominal obesity. Our lead MetAP2 inhibitor in this class of molecules is called ZGN-839. We plan to advance multiple candidate drugs into early development to establish clinical proof of concept, safety and tolerability of these molecules as a way to leverage our internal know-how in metabolic diseases and the effects of MetAP2 inhibitors. These compounds, typified by ZGN-839, could provide additional short-term value to our company through focused development partnerships and collaborations.

Mechanism of Action

Beloranib is a novel, first-in-class injectable small molecule therapy with a unique mechanism of action that reduces hunger while stimulating the use of stored fat as an energy source. Beloranib is the first new anti-obesity agent with the potential to address two important abnormalities that are present in the obese patient—hunger that is inappropriate relative to the amount of energy stored as fat and dysregulation of fat metabolism, which causes more fat to be made and stored in an obese patient than in a lean person.

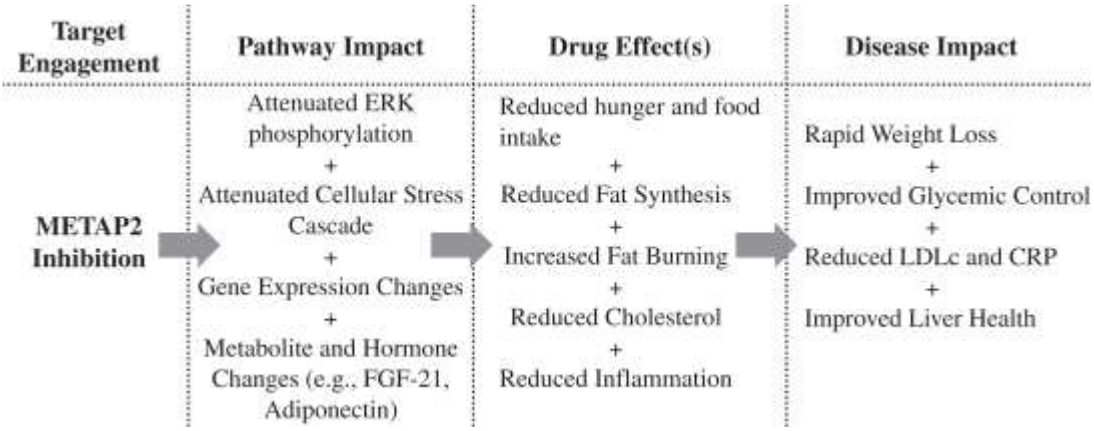
Beloranib is a potent inhibitor of MetAP2, an enzyme that modulates the activity of key cellular processes that control metabolism. MetAP2 inhibitors work, at least in part, by directing MetAP2 binding to cellular stress mediators, and, thus, reducing fat synthesis by the liver and fat storage throughout the body. In this manner, MetAP2 inhibition increases metabolism of fats as an energy source. MetAP2 inhibitors also reduce hunger and food intake by novel mechanisms that require further study to be fully understood.

Beloranib was evaluated for its 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 also was 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.

The MetAP2 inhibitor fumagillin, a structural analog of beloranib, was shown in 2004 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. Several hormones well-documented to be involved in energy metabolism are affected by beloranib, including leptin, adiponectin and fibroblast growth factor-21. These hormones are thought to contribute to the weight-reducing effects of beloranib and also are known to be involved in control of body weight, fat metabolism and glucose metabolism. This series of mechanistic effects leads to rapid and sustained reduction of excess body weight with beloranib treatment, such as has been observed in animal studies and our clinical trial experience to date.

Our clinical experience to date shows that beloranib treatment is also associated with improvements in cardiovascular disease risk factors such as plasma total cholesterol, high density lipoprotein cholesterol, or HDL, and C-reactive protein, or CRP. Plasma total cholesterol, HDL, CRP, and systolic blood pressure are considered to be the most rigorous systemic biomarkers of cardiovascular disease risk. Our clinical experience to date with beloranib suggests that its use is not associated with an increase in blood pressure or heart rate, which makes it particularly relevant to severely obese patients, in whom a broad spectrum of elevated cardiovascular risk factors often is seen.

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



Clinical Trials

Beloranib was initially formulated for intravenous administration to facilitate early clinical efforts. Our clinical program has been oriented to first establish whether beloranib would lead to weight loss at tolerated and safe doses, and then to transition to the more convenient subcutaneous injection method of administration for development in our indications of interest, including PWS, HIAO and severe obesity.

We have completed six clinical trials evaluating beloranib in over 200 patients. Our first three clinical trials, ZAF-001, ZAF-003 and ZAF-101, established a working dose range for beloranib above 0.65 mg and below 3 mg. To further explore the efficacy, safety, tolerability and impact of beloranib on severe obesity, we conducted ZAF-201, a 12-week clinical trial of beloranib administered by subcutaneous injection twice weekly to 124 obese patients at doses of 0.6 mg, 1.2 mg, and 2.4 mg. This placebo-controlled, double-blinded trial, established that the efficacy of beloranib continued beyond four weeks and was associated with sustained impact on key biomarkers of effect.

These clinical trials set the stage for continued evaluation of beloranib, by subcutaneous administration, in patients with PWS and HIAO. ZAF-211 was a placebo-controlled, double-blinded trial evaluating safety and tolerability as well as the effects of 1.2 mg or 1.8 mg doses of beloranib in patients with PWS on body weight, body composition and hyperphagia-related behaviors. ZAF-221 was a randomized, double-blind placebo-controlled trial comparing the effects of a 1.8 mg dose of beloranib versus placebo on body weight, body composition and hunger and related parameters in patients with HIAO.

The table below summarizes the structure of and key findings from these six clinical trials of beloranib.

Trial Number	Brief Description	Treatment Duration	BMI Range of Patients (kg/m ^{2})	Observations
ZAF-001 *Phase 1b*	• Randomized, double-blind, placebo-controlled trial • Escalating doses of 0.1 mg/m ^{2}, 0.3 mg/m ^{2}, and 0.9 mg/m ^{2}, or approx. 0.2 mg, 0.6 mg, and 2 mg • 1-hour intravenous infusion twice weekly	4 weeks	32-45	• Dose dependent weight reductions with 0.9 mg/m2 twice weekly resulting in -3.6 kg weight loss versus -1.2 kg change with placebo over 4 weeks • Metabolic benefits (C-reactive protein and metabolic hormones) observed in dose dependent fashion • Safe and well tolerated at all dose levels

ZAF-003
Phase 1b
	• Randomized, double-blind, placebo-controlled trial
	• Static dosing scheme of 3.0 mg, 6.0 mg, and 2.5 mg
	• 1-hour intravenous infusion
	  • 3.0 mg and 6.0 mg doses given twice weekly for 4 weeks
	  • 2.5 mg dose given twice weekly for the first week and once weekly for the subsequent 6 weeks.
		4 weeks or 7 weeks	30-50	• Dose dependent weight reductions with 6.0 mg dose resulting in -6.7 kg weight loss, 3.0 mg in -4.7 kg, and placebo in -0.3 kg over 4 weeks
				• Once weekly 2.5 mg dose resulted in weight loss of -3.1 kg over 7 weeks and with greater variability
				• 6.0 mg not very well tolerated with gastrointestinal side effects and sleep disturbance emerging as dose limiting adverse effects; Doses of 3.0 mg or lower were well tolerated and effective
				• Once-weekly regimen was less effective than bi-weekly administration

ZAF-101 *Phase 1b*	• Randomized, double-blind, placebo-controlled trial • 1.0 mg, 2.0 mg, and 4.0 mg were evaluated • Subcutaneous injection twice weekly	4 weeks	30-45	• Significant weight reduction with all doses; 4.0 mg dose resulting in -6.1 kg, 2.0 mg in -4.2 kg, 1.0 mg in -4.3 kg, and placebo in -1.2 kg • Comparable metabolic benefits observed as in prior trials, including body composition improvements; sense of hunger reduced with all doses • 4.0 mg not as well tolerated with similar adverse event profiles as with 6.0 mg intravenous dose in ZAF-003 – mainly gastrointestinal side effects and sleep disturbances; injection site adverse events unremarkable

Trial Number	Brief Description	Treatment Duration	BMI Range of Patients (kg/m ^{2})	Observations
ZAF-201 *Phase 2a*	• Randomized, placebo controlled, double-blinded, parallel design trial • Fixed beloranib doses including 0.3 mg, 0.6 mg, 1.2 mg, 2.4 mg, and 3.2 mg or placebo • Subcutaneous injections twice weekly	12 weeks	30-50	• 0.3 mg not effective, 3.2 mg not well tolerated; both doses eliminated after first 2-4 weeks of dosing (pre-defined) • Progressive and dose dependent weight reduction; -10.9 kg in the 2.4 mg group, -6.9 kg in the 1.2 mg group, -5.5 kg in the 0.6 mg group, versus -0.4 kg in placebo • Comparable metabolic and body composition benefits observed as with prior studies • Most adverse events, including sleep disturbances, mild-moderate and transient
ZAF-211 *Phase 2a*	• Randomized, double-blind, placebo-controlled parallel design trial • 1.2 mg and 1.8 mg doses of beloranib or placebo in patients with PWS • Subcutaneous injections twice weekly	4 weeks	26-44	• Trend toward reduction in body weight measured by scale weight; -1.27% in beloranib-treated patients (pooled analysis of 1.2 and 1.8 mg treatment groups) versus +0.34% change in placebo-treated patients • Reduction in body mass assessed by dual-energy x-ray absorptiometry, or DEXA; -2.1% in beloranib-treated patients versus +2.0% change in placebo-treated patients • Reduction in total fat mass assessed by DEXA; -2.9% in beloranib-treated patients versus +3.6% change in placebo-treated patients • Reduction in hyperphagia related behaviors (at 1.8 mg dose level only).
ZAF-221 *Phase 2*	• Randomized, double-blind, placebo-controlled design trial • 1.8 mg dose of beloranib or placebo in patients with HIAO • Subcutaneous injections twice weekly	4 weeks with 4 week extension	30-55	• We observed mean weight loss of 3.4 kg and 6.2 kg in patients with HIAO after 4 and 8 weeks of treatment with beloranib, respectively, in contrast to 0.3 kg mean weight loss in patients treated with placebo for 4 weeks • Safe and well tolerated at all dose levels

Across all our clinical trials, beloranib has been well-tolerated at doses we would expect to explore in the future. There have been no serious adverse events, or SAEs, attributed to beloranib in our completed clinical trials. The main adverse events, or AEs, including those leading to drop-outs, in patients dosed with beloranib have been sleep disturbances, principally manifested as delayed onset of sleep, nausea and vomiting. For certain of our clinical trials, we performed statistical analysis of our results and report the p-value, which is a statistical calculation that relates to the probability that a difference between groups happened by chance, with a p-value of less than 0.05 (i.e., less than 5% probability that the difference happened by chance) generally being used as the threshold to indicate statistical significance. We expect that the FDA will perform its own independent statistical analyses to determine if our data support regulatory approval. Each of our clinical trials is discussed in more detail below.

Phase 1b Clinical Trials

ZAF-001—A Randomized, Double-Blind, Placebo-Controlled Multiple Dose Study, to Assess Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of ZGN-433 (Beloranib for Intravenous Infusion) in Obese Volunteers

ZAF-001 was a four-week double-blind, placebo controlled, dose escalation and multiple dose trial conducted in Australia. The primary clinical endpoints of this clinical trial were safety, tolerability, pharmacokinetics and pharmacodynamics of beloranib administered by intravenous administration. 31 Caucasian female patients, with an average age of 52.2 years and BMI range of 32-45 kg/m ^{2}, were enrolled in this clinical trial. 22 patients received beloranib and nine patients received placebo. The patients were divided into three different cohorts, with each cohort receiving 0.10 mg/m ^{2}, 0.30 mg/m ^{2}, or 0.90 mg/m ^{2} of beloranib or placebo via intravenous infusion twice weekly for four weeks. The primary objectives of this clinical trial were to (i) evaluate the safety and tolerability of beloranib in obese patients and (ii) determine the plasma pharmacokinetics and pharmacodynamics of beloranib in obese patients. A secondary objective was to obtain information on weight loss in obese patients exposed to beloranib for eight intravenous doses over a one-month period. A total of 26 of the 31 enrolled patients completed this clinical trial as planned, receiving all eight infusions of study drug. Three placebo patients and two beloranib-treated patients withdrew from this clinical trial because of loss of venous access and other reasons unrelated to drug treatment.

The key results of this clinical trial are summarized for the Per Protocol population, patients completing the full dosing period and receiving a minimum of six doses, as follows:

4-week Phase 1b Proof of Concept Clinical Trial in Obese Patients (ZAF-001)

Trial Arm	Number of Patients Per Protocol	Baseline Body Weight (kg)	Average Weight Change (kg)	p-value*
Placebo	6	96.0	-1.2	—
Beloranib 0.1 mg/m ^{2}	6	105.3	-0.9	—
Beloranib 0.3 mg/m ^{2}	6	100.3	-1.3	—
Beloranib 0.9 mg/m ^{2}	8	104.2	-3.6	—

* statistical analysis was not performed in this proof of concept trial

- Post hoc analyses suggested that beloranib had favorable effects on other parameters, including body fat content, C-reactive protein, low density lipoprotein cholesterol and hunger.

There were no drug-related SAEs or treatment emergent adverse events, or TEAEs. Headaches and gastrointestinal symptoms were the most common TEAEs in all groups including placebo and tended to be mild in intensity and transient. Contusions or bruising which occurred at infusion sites, often due to difficulty in IV access, were reported. There were no clinically significant changes reported as TEAEs in hematology, serum chemistry or urinalysis values for any of the patients in any of the dose groups. The objectives of this clinical trial were met. Weight loss was a secondary clinical endpoint and was not subjected to statistical analysis.

ZAF-003—Phase 1b Trial of Beloranib, a Novel Methionine Aminopeptidase 2 (MetAP-2) Inhibitor for Treatment of Extreme Obesity: Randomized, Double-Blind, Placebo-Controlled, Escalating Doses in Female Volunteers

ZAF-003 was a double-blind, placebo controlled, dose escalation and multiple dose trial conducted in Australia. A static dosing scheme of 3.0 mg, 6.0 mg, and 2.5 mg was evaluated and all doses were administered via 1-hour intravenous infusion, with 3.0 mg and 6.0 mg doses given twice weekly for four weeks, and the 2.5 mg dose given twice weekly for the first week and once weekly for the subsequent six weeks for total of seven weeks of treatment. Patients who qualified after the screening round were randomized 2:1 to treatment with beloranib or placebo. 25 obese female patients were enrolled, and 22 patients completed this clinical trial. Three patients withdrew from this clinical trial, two from the 6.0 mg treatment group, due to tolerability limitations and one from the 2.5 mg treatment group due to an adverse event deemed not to be related to study drug. 92% of the patients were Caucasian, 4% of the patients were Asian and 4% of the patients were Pacific Islanders. The average ages were between 44.0 and 51.3 years for the various treatment groups. The primary objective of this clinical trial was to demonstrate safe doses of intravenous infusion of beloranib for reduction of body weight in female obese patients with baseline BMIs ranging from 30 to 50 kg/m ^{2} . The secondary objectives of this clinical trial were to (i) confirm the safety profile of beloranib in obese female patients receiving incrementally larger fixed doses than the dose regimen previously tested in ZAF-001, (ii) evaluate the tolerance, weight loss and ease of administration for continuing a safe dose of beloranib on a weekly schedule, (ii) correlate higher dose levels of beloranib with measures of reduction in body weight and hunger, (iii) confirm the pharmacokinetic profile of beloranib, and (iv) correlate exposure of beloranib with changes in biomarkers for fasting plasma lipids, lipid metabolism, fasting insulin and thyroid function.

The key results of this clinical trial are summarized for the Per Protocol population, patients completing the full dosing period and receiving a minimum of six doses, as follows:

4-week Phase 1b Proof of Concept Clinical Trial in Obese Patients (ZAF-003)

Trial Arm	Number of Patients Per Protocol	Baseline Body Weight (kg)	Average Weight Change (kg)	p-value*
Placebo	8	104.6	-0.1	—
Beloranib 3.0 mg twice weekly	6	102.3	-4.7	—
Beloranib 6.0 mg twice weekly	3	105.5	-6.7	—
Beloranib 2.5 mg once weekly	5	94.0	-2.7	—

* statistical analysis was not performed in this proof of concept trial

- Post hoc analyses suggested that beloranib had favorable effects on other parameters, including body fat content, C-reactive protein, low density lipoprotein cholesterol and hunger.

The primary and secondary objectives of this clinical trial were met, showing the maximally tolerated dose of 3.0 mg of beloranib administered by intravenous infusion was identified, weight loss was uniformly observed at both 3.0 mg and 6.0 mg dose levels of beloranib, and a visual analog scale of hunger revealed reduction in hunger at both doses. Further, a once-weekly regimen was evaluated with 2.5 mg of beloranib, which was well-tolerated and showed limited evidence of weight loss efficacy or reduction in hunger despite being well-tolerated.

ZAF-101- ZGN-440 (Beloranib for Subcutaneous Injection), A Novel Methionine Aminopeptidase 2 Inhibitor for Treatment of Obesity: A Randomized Double-Blind Placebo Controlled Dose Escalation Phase 1b Trial to Evaluate Safety, Pharmacokinetics, Pharmacodynamics and Initial Weight Loss

ZAF-101 was a four-week, multi-dose trial using beloranib formulated for subcutaneous, or SC, injection in obese, otherwise healthy females, conducted in Australia. This clinical trial was a double-blind, placebo controlled, dose escalation and multiple dose study. Doses of 1.0 mg, 2.0 mg, and 4.0 mg of beloranib were

evaluated and all doses were administered by SC injection twice weekly for four weeks. Patients who qualified after the screening were randomized 1:1:1:1 to treatment with the three dose levels of beloranib or placebo. 25 female Caucasian patients were enrolled. Four patients withdrew from this clinical trial, three from the 4.0 mg treatment group and one from the 2.0 mg treatment group due to sleep disturbance. The average ages were 46.0 to 49.9 years for the various treatment groups and the BMI range of the patients was 30-45 kg/m^2. This clinical trial was designed to evaluate the safety and tolerability of beloranib administered SC in obese female patients. Secondary objectives of this clinical trial were to assess weight loss and responses in metabolic biomarkers over a dose range of beloranib in obese female patients and to compare weight loss due to beloranib administered SC to that previously observed by beloranib administered intravenously.

The key results of this clinical trial are summarized for the Per Protocol population, patients completing the four-week dosing period and receiving a minimum of six doses, as follows:

4-week Phase 1b Proof of Concept Clinical Trial in Obese Patients (ZAF-101)

Trial Arm	Number of Patients Per Protocol	Baseline Body Weight (kg)	Average Weight Change (kg)	p-value
Placebo	6	97.3	-1.2	—
Beloranib 1.0 mg	6	99.1	-4.3	<0.001
Beloranib 2.0 mg	5	92.7	-4.2	<0.001
Beloranib 4.0 mg	4	93.9	-6.1	<0.001

There were no clinically significant changes in laboratory parameters, electrocardiograms, or vital signs with any of the doses. There were no deaths or severe AEs reported in this clinical trial. Aside from mild and transient injection site reactions, which were observed across all treatment groups, including placebo, SC administration of the drug appeared to be locally well-tolerated. However, the highest dose, or 4.0 mg of beloranib, appeared to be less well-tolerated systemically and led to more frequent moderate intensity TEAEs and premature trial withdrawals, mainly due to gastrointestinal events and sleep disturbance. Sleep disturbance AEs were reported by 100% of subjects in the 2.0 mg group (6 events), 85.7% of subjects in the 4.0 mg group (6 events), 83.3% of subjects in the 1.0 mg treatment group (5 events) and 16.7% of subjects in the placebo treatment group (1 event). All events of sleep disturbance were deemed to be probably related to study drug. Abnormal dreams, mostly vivid dreams, were the other frequently reported sleep abnormalities reported as TEAEs reported by 83.3% of subjects in the 2.0 mg dose group, 85.7% in the 4.0 mg dose group and 66.7% in the 1.0 mg dose group. No subjects reported abnormal dreams in the placebo group. The majority of sleep disorders were of mild severity—83.3% in the 2.0 mg dose group, 33.3% in the 4.0 mg dose group, 100% in the 1.0 mg dose group; as were the majority of abnormal dreams—83.3% in the 2.0 mg dose group, 85.7% in the 4.0 mg dose group, and 66.7% in the 1.0 mg dose group. All remaining events were moderate in severity. A total of four subjects including one subject in the 2.0 mg dose group and three subjects from the 4.0 mg dose group withdrew from the trial due to sleep disturbance. The increased incidence of early trial withdrawal due to sleep disturbance in the 4.0 mg treatment group suggested that this dose was less well tolerated. Gastrointestinal disorders were frequently reported across all dose groups. The greatest percentage of subjects to report gastrointestinal adverse events, such as diarrhea and nausea, were in the placebo group, 50.0% (3 events in 3 subjects) and 33.3% (2 events in 2 subjects), respectively. Occurrence of diarrhea in beloranib-treated subjects ranged between 16.7% (1 event in 1 subject) for the 2.0 mg dose group, and 42.9% (3 events in 3 subjects) in the 4.0 mg dose group. Occurrence of nausea in beloranib-treated subjects ranged from 14.3% (1 event in 1 subject) for the 4.0 mg dose group, and 16.7% (1 event in 1 subject) in both the 1.0 and 2.0 mg dose groups.

Phase 2a Clinical Trials

ZAF-201—Randomized, Double-Blind, Placebo-Controlled, Dose Ranging Phase 2 Trial of Beloranib (ZGN-440 for Subcutaneous Injection), A Novel Methionine Aminopeptidase 2 Inhibitor, in Obese Subjects to Evaluate Weight Reduction, Safety, and Pharmacokinetics Over 12 Weeks

ZAF-201 was a 12-week Phase 2a proof-of-concept clinical trial in 160 obese patients, of whom 122 were dosed with beloranib, across eight participating trial sites in Australia. 93.8% of patients were female, 97.5% were Caucasian, the average age was 48.4 years and patients had a BMI range of 30-54 kg/m ^{2}. Patients were excluded from this clinical trial if they had been involved recently in another weight loss trial, or if they had clinically significant liver, renal, pulmonary, cardiovascular, oncologic, gastrointestinal disease, or severe mental illness. This clinical trial was designed to evaluate weight loss and responses in metabolic biomarkers over a dose range of beloranib and to assess safety and tolerability of beloranib over 12 weeks in obese patients. This was a randomized, placebo controlled, double-blinded, parallel design trial to evaluate a range of fixed beloranib doses, including 0.3 mg, 0.6 mg, 1.2 mg, 2.4 mg and 3.2 mg, in comparison to placebo. All doses were administered as SC injections twice weekly for 12 weeks.

Trial endpoints included safety and tolerability, weight loss, body composition by bio-impedence, pharmacokinetic, or PK, and pharmacodynamic assessment. As stipulated in the protocol, our Safety Review Committee for this clinical trial, or SRC, reviewed interim safety and PK results after 36 patients from the initial part of this clinical trial completed at least 2 weeks of treatment. Laboratory, electrocardiogram, and vital sign reviews were deemed to be unremarkable and lacking any significant safety concerns. The SRC recommended to eliminate the lowest and highest active dose groups, 0.3 mg and 3.2 mg, thus leaving the doses of 0.6 mg, 1.2 mg, 2.4 mg or placebo to be studied in the remainder of this clinical trial. This was based on the conclusion that the weight loss for the 0.3 mg dose was not clinically meaningful and the 3.2 mg dose was not well-tolerated. The most common AE leading to early termination at the 2.4 mg and 3.2 mg dose levels was sleep disturbance.

As severely obese patients are at an increased risk for cardiovascular disease, we measured systemic biomarkers of cardiovascular disease risk, including low density lipoprotein cholesterol, HDL, CRP, trigylcerides and blood pressure in trial participants, to determine beloranib's impact on such biomarkers. The results of these biomarker measurements in this trial, as summarized below, suggest that beloranib treatment does not increase the risk of cardiovascular disease and may be associated with reduced cardiovascular disease risk. While we plan to include biomarkers of cardiovascular disease risk as an endpoint for our planned Phase 2b clinical trial of beloranib as a treatment for severe obesity in the general population, this trial will not be designed to establish the impact of beloranib treatment on cardiovascular disease risks.

The key results of this trial are summarized for the Per Protocol population, patients completing the 12-week dosing period and receiving a minimum of 16 of 24 doses, as follows:

12-week Phase 2a Proof of Concept Clinical Trial in Obese Patients (ZAF-201)

Trial Arm	Number of Patients Per Protocol	Baseline Body Weight (kg)	Mean Weight Change (kg)	Percent Placebo-Adjusted Weight Change	p-value
Placebo	36	102.3	-0.4	—	—
Beloranib 0.6 mg	34	102.6	-5.5	-5.0	<0.0001
Beloranib 1.2 mg	31	102.6	-6.9	-6.4	<0.0001
Beloranib 2.4 mg	15	102.2	-10.9	-10.3	<0.0001

- Levels of the cardiovascular disease risk marker C-reactive protein were reduced by an average of 2.5, 2.3 and 1.9 µg/ml, or 23%, 22% and 37%, respectively, for patients treated with beloranib at 0.6 mg, 1.2 mg and 2.4 mg, respectively, compared to an average increase of 1.0 µg/ml for patients dosed with placebo (p<0.0001).

- Levels of low density lipoprotein cholesterol, or LDL-c, were reduced by an average of 0.3, 0.5 and 1.0 mmol/l, or 9.4%, 14.5% and 29.7%, respectively, for patients treated with beloranib at 0.6 mg, 1.2 mg and 2.4 mg, respectively, compared to an average reduction of 0.3 mmol/l for patients dosed with placebo ($p<0.001$ for patients treated with 2.4 mg beloranib).
- Levels of high density lipoprotein cholesterol, or HDL-c, were increased by an average of 0.1, 0.1 and 0.2 mmol/l, or 7.6%, 11.6% and 14.6%, respectively, for patients treated with beloranib at 0.6 mg, 1.2 mg and 2.4 mg, respectively, compared to no change for patients dosed with placebo ($p<0.05$ for patients treated with 1.2 mg and 2.4 mg beloranib).
- Levels of triglycerides were reduced by an average of 0.2, 0.3 and 0.4 mmol/l, or 8.8%, 9.0% and 20.3%, respectively, for patients treated with beloranib at 0.6 mg, 1.2 mg and 2.4 mg, respectively, compared to a reduction of 0.3 mmol/l for patients dosed with placebo ($p<0.05$ for patients treated with 1.2 mg and 2.4 mg beloranib).
- Systolic blood pressure was reduced by an average of 6.3 mmHg, 6.3 mmHg and 13.6 mmHg for patients treated with beloranib at 0.6 mg, 1.2 mg and 2.4 mg, respectively, compared to an average of 1.4 mmHg reduction for patients dosed with placebo ($p<0.05$ for 1.2 mg and 2.4 mg doses). Trends toward reduction in diastolic blood pressure also were observed, although these changes did not reach statistical significance.
- Sense of hunger was reduced by an average of 1.5 cm, 2.2 cm and 3.3 cm (out of a maximum number of 10 cm using a standardized visual analog scale asking how hungry the participant had been over the prior trial days) and compared to an average reduction of 0.1 cm in placebo, respectively ($p<0.05$ for all doses). Baseline values were, on average, 5.0 cm, 5.3 cm, 5.8 cm and 6.4 cm for placebo, for doses of 0.6 mg, 1.2 mg and 2.4 mg of beloranib, respectively.
- Post hoc analyses suggest that beloranib also may have favorable effects on body fat content.

While results from this clinical trial showed that beloranib doses ranging from 0.6 mg to 2.4 mg administered by SC injection resulted in dose-related weight loss, the highest dose, 2.4 mg, was associated with the most significant and rapid onset of weight loss whereas the lower doses, 0.6 mg and 1.2 mg, tended to result in slower initiation of weight reduction. However, the highest dose, 2.4 mg, of beloranib appeared to be less well-tolerated systemically and led to more frequent severe intensity TEAEs. 21 patients treated with 2.4 mg beloranib prematurely withdrew from the trial, mainly due to sleep disturbance reflective of increased sleep latency, the time patients reported taking to fall asleep at night. There were no deaths or any SAEs deemed to be possibly, probably, or definitely related to beloranib, although there were two serious thrombotic adverse events which, while not attributed to beloranib treatment, may point to the utility of assessment of prior history of thrombotic events in patients enrolled in subsequent trials and added vigilance for AEs related to blood clotting during future clinical trials. The most commonly reported TEAEs were gastrointestinal disorders, mainly nausea, diarrhea, or vomiting, nervous system disorders, mainly dizziness, and psychiatric disorders, mainly insomnia, sleep disorder, or abnormal dreams. TEAEs were generally mild in severity and transient. Other frequently reported TEAEs were headaches and injection site bruising/itching, although the incidences were comparable to placebo and not observed to be dose-related. Laboratory assessments, vital signs and electrocardiograms revealed no unexplained abnormalities or clinically significant trends. The primary objectives of this clinical trial were met, including demonstration of continued weight loss beyond the four-week trial duration evaluated in prior trials, demonstration of the tolerability profile at effective doses, and demonstration of reductions in key cardiometabolic risk parameters and hunger as well as improved body composition (reduced waist circumference and fat mass) as assessed by bioelectrical impedance.

ZAF-211—Randomized, Double-Blind, Placebo Controlled, Parallel Dose Ranging Phase 2a Trial of ZGN-440 (for Subcutaneous Injection), A Novel Methionine Aminopeptidase 2 Inhibitor, in Over-weight and Obese Subjects with Prader-Willi Syndrome to Evaluate Weight Reduction, Food-related Behavior, Safety, and Pharmacokinetics Over 4 Weeks Followed by Optional 4-Week Open-Label Extension

Our Phase 2a clinical trial of beloranib as a potential treatment of PWS was designed as a randomized, double-blind, and parallel comparison of each of 1.2 mg and 1.8 mg dose levels of beloranib, and placebo. 17 adult patients with PWS living in closely-controlled PWS-specific group homes were randomized to one of the three dosing arms, with 6, 5, and 6 patients being randomized to placebo, 1.2 mg beloranib and 1.8 mg beloranib treatment. During the course of the trial, including a two week placebo run-in phase, daily calorie allowances were increased in all patients by 50 percent to drive modest weight gain and simulate the greater access to food experienced in the general PWS population living in family home situations. All patients completed randomized treatment. The primary objectives of this clinical trial were to (i) assess the safety and tolerability of beloranib administered twice weekly SC in patients with PWS, (ii) assess body weight change, changes in body mass and fat content by DEXA, scan analysis, and responses in metabolic biomarkers over a dose range of beloranib, and (iii) evaluate changes in quality of life, PWS- specific hyperphagia-related behaviors and/or psychiatric status. The secondary objective of this clinical trial is to evaluate pharmacodynamics and apparent bioavailability over a dose range of beloranib. The randomized treatment period was followed by an optional open-label extension offering patients the opportunity to continue for an additional four weeks of treatment with 1.8 mg beloranib.

The key results of this clinical trial are summarized as follows. Both doses of beloranib have been combined as shown below, as a component of the pre-specified statistical analysis:

Four-Week Phase 2a Proof of Concept Clinical Trial in Patients with Prader-Willi Syndrome (ZAF-211)

Endpoint	Placebo Baseline (N=6)	Placebo Change (%)	Beloranib Baseline (N=11)	Beloranib Change (%)	p value (Beloranib vs. Placebo)
Body weight (kg) (Scale weight)	70.1	0.34	72.0	-1.3	0.17*
Body mass (kg) (DEXA)	69.7	2.0	72.1	-2.1	0.002
Fat mass (kg) (DEXA)	31.1	3.6	34.6	-2.9	0.013

* not statistically significant by ANCOVA, or analysis of covariance, a pre-specified statistical analysis, used to assess changes in all key endpoints. ANCOVA is a standard statistical test that takes into account the baseline measurements for each subject.

- Levels of high density lipoprotein cholesterol were increased by an average of 26% in beloranib-treated patients, compared to an average increase of 1% in patients dosed with placebo (p=0.005).
- Levels of low density lipoprotein cholesterol were reduced by an average of 27% in beloranib-treated patients, compared to an average increase of 3% in patients dosed with placebo (p=0.005).
- Hyperphagia related behaviors typical of patients with PWS were reduced by an average of 52.4% by treatment with 1.8 mg beloranib, compared to an average increase of 40.5% in patients dosed with placebo and an average increase of 1.8% in patients treated with 1.2 mg beloranib. The change in behavior was statistically significant from baseline for the patients treated with 1.8 mg beloranib (not statistically significant by ANCOVA; p=0.025 by post hoc paired t-test).

There were no clinically significant changes in laboratory parameters, electrocardiograms and vital signs with any of the doses. There were no deaths, SAEs, or severe AEs reported in this clinical trial. Aside from mild and transient injection site reactions, which were observed across all treatment groups, including placebo, SC administration of the drug appeared to be locally well-tolerated.

Unlike patients with severe obesity in the general population, patients with PWS are missing the function of multiple genes. In order to determine if the underlying mechanistic pathway of beloranib was engaged in patients

with PWS, we measured levels of low density lipoprotein cholesterol and fat mass. MetAP2 inhibitors, such as beloranib, work, at least in part, by directing MetAP2 binding to cellular stress mediators, and, thus, reducing fat synthesis by the liver and fat storage throughout the body, leading to a reduction in cholesterol, evidenced by reduced levels of low density lipoprotein cholesterol and reduced fat mass. In this clinical trial, patients with PWS treated with beloranib had both reduced levels of low density lipoprotein cholesterol and fat mass, suggesting that patients with PWS respond to beloranib treatment in a similar manner as severely obese patients that are not missing the function of multiple genes. Likewise, while exploratory, salutary effects on behaviors were observed, which reached clinical significance for the 1.8 mg beloranib treatment arm. These behavioral changes include a range of aspects of the PWS phenotype recorded by the caregiver-administered hyperphagia-related behavior questionnaire, an instrument that measures the frequency and severity of behavioral issues typical of patients with PWS that we are currently validating with the FDA for support of our pivotal trials.

ZAF-221—Randomized, Double-Blind, Placebo Controlled, Phase 2 Trial of ZGN-440 (Subcutaneous Beloranib in Suspension), A Novel Methionine Aminopeptidase 2 Inhibitor, in Obese Subjects with Hypothalamic Injury to Evaluate Weight Reduction and Safety Over 4 Weeks Followed by an Optional 4-Week Open-Label Extension

Our Phase 2 clinical trial of beloranib as a potential treatment of HIAO was designed as a randomized, double-blind, and parallel comparison of 1.8 mg of beloranib and placebo. This clinical trial was conducted at four trial sites, two in the United States and two in Australia. 14 adult patients, nine female and five male, with magnetic resonance imaging confirmed hypothalamic injury and rapid weight gain following resection of craniopharyngioma (n=13) or pituitary macroadenoma (n=1) were randomized to one of the two dosing arms in a 3:4 ratio, with six and eight patients being randomized to placebo and 1.8 mg beloranib treatment, respectively. The average age of patients was approximately 32 years with an average BMI of 43 kg/m ^{2} . All patients assigned to beloranib treatment completed randomized treatment, while one patient assigned to placebo discontinued treatment due to apparent sensitivity to the placebo injectate. The primary objectives of this trial were to (i) assess the safety and tolerability of beloranib administered twice weekly SC, and (ii) assess weight loss effects of beloranib in obese patients with HIAO. The secondary objectives of this trial were to evaluate changes in quality of life and hunger in obese patients with HIAO who have received beloranib, and to assess responses in metabolic biomarkers and plasma exposure to beloranib in obese patients with HIAO. The randomized treatment period was followed by an optional open-label extension offering patients the opportunity to continue for an additional four weeks of treatment with 1.8 mg beloranib.

The key results of this trial are summarized as follows:

Four-Week Phase 2 Proof of Concept Trial in Patients with Hypothalamic Injury-Associated Obesity (ZAF-221)

Trial Arm	Number of Patients Per Protocol Population	Baseline Body Weight (kg)	Average Weight Change during Randomized Treatment (kg)	p-value (for randomized treatment period)	Average Weight Change from Baseline to End of Open Label Extension (kg)
Placebo	4	128.0	-0.3	—	-3.0*
Beloranib 1.8 mg twice weekly	8	118.7	-3.4	0.01	-6.2

* Patients randomized to placebo received beloranib 1.8 mg twice weekly during the open label extension.

Beloranib was well-tolerated in this trial. No consistent new or unanticipated safety issues arose during the course of treatment. There were no deaths or serious adverse events reported in this trial. There were no early trial discontinuations in patients treated with beloranib. Key tolerability findings were mild dizziness.

The results of this trial suggest that beloranib treatment leads to a similar rapid pace of weight loss in patients with disrupted hypothalamic structures, and therefore provides, further support for the extra-hypothalamic mode of action of beloranib, as well as its differentiation from other weight loss agents that target hypothalamic neuronal activity.

Clinical Trial Summary

Our clinical trials suggest that administration of beloranib by IV infusion twice weekly for four weeks, or eight doses, at dose levels of up to 3.0 mg was safe and well-tolerated. The incidence and severity of AEs was similar across all dose groups in this range. While these clinical trials were of short duration and designed to demonstrate safety and tolerability, significant decreases in body weight and large decreases in sense of hunger were observed in beloranib-treated patients when compared to the placebo group. Additional clinical trials of longer-term treatment with beloranib designed to demonstrate efficacy are required before we can submit an NDA for beloranib as a treatment for any indication that we are pursuing. In our ongoing Phase 2b clinical trial of beloranib as a treatment for severe obesity in the general population and our ongoing Phase 3 clinical program of beloranib as a treatment for patients with PWS, patients are being treated with beloranib for a substantially longer period of time than as treated in our earlier clinical trials. A SC formulation of beloranib for human use was developed and completed human testing in a Phase 1b clinical trial, which showed that doses ranging from 1.0 mg to 4.0 mg administered by SC injection resulted in statistically significant dose-related weight loss. While the highest dose of 4.0 mg was associated with the most significant weight loss, it appeared to be less well-tolerated systemically and led to more frequent moderate intensity TEAEs and premature trial withdrawals, mainly due to gastrointestinal events and sleep disturbance. There have been no deaths or drug-related SAEs. Laboratory safety measures, vital signs and electrocardiograms have been unremarkable in all completed clinical trials for all doses tested. A 12-week Phase 2a clinical trial, ZAF-201, using subcutaneously administered doses of 0.6 mg, 1.2 mg and 2.4 mg of beloranib has confirmed these earlier observations, and we have observed continued weight loss with maintenance of the key favorable drug effects on body composition, hunger and C-reactive protein levels. A further salutary effect on blood pressure has been identified, strengthening our view that beloranib will have a favorable impact on cardiovascular disease risk.

ZAF-211 was our first clinical trial in patients with PWS using doses of 1.2 mg and 1.8 mg beloranib administered by subcutaneous injection twice weekly for four weeks. This initial clinical trial has generated promising results, with beloranib-treated patients showing reductions in body mass and body fat content, along with improvements in hyperphagia-related behavior. ZAF-221 was our first clinical trial in patients with HIAO using 1.8 mg beloranib administered by subcutaneous injection. This initial clinical trial in patients with HIAO, similar to our Phase 2a clinical trial in patients with PWS, has generated promising results, with beloranib-treated patients showing reductions in placebo-adjusted body weight. Taken together with the results of our previous clinical trials, we believe there is a very compelling basis for continued development of beloranib for the treatment for rare conditions such as PWS and HIAO, where obesity is a co-morbidity of an underlying condition, and severe obesity in the general population.

Next Steps

Pivotal Phase 3 Program of Beloranib for the Treatment of Patients with PWS

Based on discussions with the regulatory authorities to date, we currently expect that our pivotal Phase 3 clinical program will consist of two Phase 3 clinical trials, one in the United States and the other in the European Union. In the ongoing U.S. trial, ZAF-311, we are evaluating the efficacy, safety and tolerability of 1.8 mg and 2.4 mg beloranib versus placebo over six months of randomized, double-blinded treatment in approximately 102 patients with PWS. This trial will be followed by an open label extension to allow for further evaluation of beloranib's efficacy and safety following an additional six months of treatment for those patients who have completed the six month randomized treatment period and who agree to remain on treatment.

The European trial, ZAF-312, is projected to evaluate the efficacy, safety and tolerability of 2.4 mg beloranib versus placebo over twelve months of randomized, double-blinded treatment in approximately 150 patients with PWS. This trial will be followed by an open label extension to allow for further evaluation of beloranib's efficacy and safety following an additional six months of treatment.

Both of these trials will be conducted in outpatient settings, including patients living in family home settings and in group home settings specializing in the care of residents with developmental disabilities, and have a consistent caregiver to provide input to the assessment of hyperphagia-related behaviors.

Pivotal Phase 3 Clinical Program Endpoints

Based on our communications with the FDA and European health authorities, to support an NDA submission to the FDA and an MAA submission to the EMA, we must demonstrate in two Phase 3 clinical trials a statistically significant and clinically meaningful improvement in either (i) hyperphagia-related behaviors or (ii) total body weight in patients treated with beloranib compared to patients receiving placebo. In order to assess efficacy of these dual endpoints, each will be evaluated for treatment effect of beloranib 2.4 mg at a significance level of p less than 0.025. If the comparison between 2.4mg and placebo is statistically significant for an endpoint, that endpoint will be evaluated for treatment effect of beloranib 1.8mg at a significance level of p=0.025.

Hyperphagia-related behaviors will be measured by a slightly modified version of the PWS-HQ that was used in our Phase 2a clinical trial of beloranib in patients with PWS. Per discussion with the FDA, this questionnaire has been revised since our Phase 2a trial to remove one question. The PWS-HQ is undergoing validation under guidance of the FDA Study Endpoints and Labeling Development staff, which we expect to be completed during the course of our Phase 3 program but prior to regulatory filing. If we fail to validate the PWS-HQ in time for it to be an effective tool to support the data from our Phase 3 clinical trial, our Phase 3 program and, in turn, our regulatory filing may be delayed until we validate the tool or develop a new one. The PWS-HQ will need to be further validated for use in multiple countries with different native languages in support of the ZAF-312 trial. This validation work may be possible outside of the context of beloranib treatment, per se, or may require additional validation in the context of beloranib treatment. Scientific advice received from the European Medecines Agency, or EMA, supported the importance of hyperphagia-related behaviors as a meaningful clinical endpoint for the PWS indication and that the ongoing approach to validation of the PWS-HQ is acceptable.

Total body fat mass, a key physical derangement of obesity that is substantially and pathologically increased in patients with PWS, will be assessed in both ZAF-311 and ZAF-312 as a key secondary endpoint, and is defined as a percentage change in body fat content as measured using DEXA from baseline to the end of randomized treatment with beloranib treatment compared to a change from baseline to end of randomized treatment in patients treated with placebo. We also will include change in total body mass, measured by DEXA, as a secondary endpoint in both of our pivotal Phase 3 clinical trials. In addition, we will include other secondary endpoints such as the evaluation of changes in key biomarkers of beloranib response, including low density lipoprotein cholesterol, high density lipoprotein cholesterol, C-reactive protein concentrations, number of active skin lesions related to skin-picking behavior, and quality of life.

In addition to efficacy endpoints, our Phase 3 clinical trial protocols assume that in order to support an NDA submission to the FDA and an MAA submission to the EMA, we must demonstrate the safety and tolerability of beloranib over one year of dosing.

Pivotal Phase 3 Clinical Program Trials' Design

Each of our pivotal Phase 3 clinical trials is a double-blinded, randomized placebo-controlled trial. We are identifying patients through interactions with physicians specializing in the medical management of PWS and to screen all patients for eligibility at their first visit. Patients who qualify for enrollment and who agree to

participate in the trial receive subcutaneous injections of beloranib or placebo twice weekly. We refer to the time at which patients are enrolled and initiate trial drug treatment as baseline.

The eligibility criteria for inclusion of patients in our pivotal Phase 3 clinical trials include the following:

- Genetically confirmed diagnosis of PWS.
- Age of at least 12 years but not older than 65 years in the United States and 50 years in the European Union.
- BMI greater than 27 kg/m ^{2} but less than 60 kg/m ^{2}, except that for patients between 12 and 18 years of age, we will require a BMI Z-score ≥ 2, which means the juveniles' BMI will be in the 95 th percentile or higher for children of their age. These BMI criteria define obesity in adult and adolescent individuals, respectively, and we believe that they encompass most patients with PWS to allow for a clear assessment of beloranib's impact on body weight and fat content. The BMI entry criteria is being reduced to 27 kg/m ^{2}, in order to enhance recruitment of the trials and to capture a more representative population of family home-based patients.
- Baseline PWS-HQ score of 13 or greater in the United States and greater than 11 in the European Union. PWS-HQ scores of 11 to 13 correspond to moderate behavioral derangement associated with hunger-related behavior typical of PWS. The possible range of scores in the PWS-HQ employed in our Phase 3 clinical trials, is 0-36. During our Phase 2a clinical trial of beloranib in patients with PWS, we observed a floor effect of the PWS-HQ in the clinical response in patients who had lower PWS-HQ scores, which indicates that the instrument may lose sensitivity to drug responses in patients with nominally expressed hyperphagia-related behaviors. As a result, we expect to only include patients with baseline scores of 13 or above in the United States and greater than 11 in the European Union. We believe this criterion will reduce variability in clinical response and further improve our ability to detect differences between the beloranib treatment groups and the placebo group for this primary endpoint.

We plan to include in our pivotal Phase 3 clinical trials those patients with type 2 diabetes, a common co-morbid condition in PWS, particularly in older patients, and those patients being treated with growth hormone, a common treatment for patients with PWS to assist in their growth and management of body composition, particularly lean body mass. As in our Phase 2a trial for PWS, ZAF-311 was initiated using single use vials for the drug product; matching placebo, and diluent. In the ZAF-311 extension trial, ZAF-312 and all subsequent Phase 2 and 3 studies, we plan to test a pre-filled diluent syringe instead of single use glass vials, which were used in our Phase 2a clinical trial.

Timing of the Planned Pivotal Phase 3 Clinical Program

We initiated our pivotal Phase 3 clinical trial in the United States in September 2014.

We anticipate that it will take at least six to nine months to fully enroll up to 102 patients with PWS in this trial. We anticipate that the six-month data from this trial will be available by early second quarter of 2016. We anticipate initiating our Phase 3 clinical trial in the European Union in the middle of 2015. After initiation, we anticipate that it will take at least six to nine months to fully enroll up to 150 patients with PWS in this trial.

As of December 31, 2014, we had ten active trial sites in the United States with plans to open five additional trial sites. We anticipate 25 trial sites in the European Union.

Other Clinical Trials

Currently we are also conducting a Phase 2b clinical trial of beloranib as a treatment for severe obesity in the general population in patients who also have type 2 diabetes. This trial is being conducted in severely obese adult patients with type 2 diabetes at 16 trial sites located in Australia. We anticipate enrolling approximately 150 patients. Patients in this trial will be treated with either beloranib or placebo for a period of 52 weeks. We are currently using a pre-filled diluent syringe instead of single use glass vials, which were used in our Phase 2a trial.

The primary efficacy endpoint of this trial is change in body weight. Secondary endpoints are proportion of patients achieving certain change in body weight benchmarks and changes in key biomarkers related to glycemic control and other cardiometabolic parameters. Interim six month data from this trial is anticipated in late 2015 or early 2016.

Pre-clinical

We have conducted toxicology studies of beloranib in support of clinical development. Dose selection and precautions for ongoing clinical trials have been informed by toxicology studies in rats, beagle dogs, and rabbits. Toxicological studies of up to six months in rat and nine months duration in dogs using single, daily or intermittent dosing have established no observed adverse effect levels at higher exposures relative to those in humans. At higher doses in rats and dogs the findings of toxicological importance were inhibition of spermatogenesis (with testicular atrophy/exfoliation of germ cells in testes/epididymides) and hematopoietic suppression including significant reductions in platelet and white blood cell counts, including lymphocytes, thymic, lymph node and splenic atrophy or lymphoid depletion, mild liver and kidney tubular epithelia cell toxicity, gastrointestinal de-epithelialization, hemorrhage/discoloration and diarrhea, and clonic convulsion. Injection site tolerability in both rats and dogs has been demonstrated with several formulations of beloranib and injection site tolerability has been corroborated in clinical trials. A T-cell dependent antibody response study in rats demonstrated that decreases in immunoglobulin responses occurred in males at doses of 0.3 mg/kg and higher, and in females at 3 mg/kg and higher. Collectively, the data indicate that beloranib may be immunosuppressive although events suggesting immunosuppression have not been noted in the clinical trials to date. We plan to measure T-cell and B-cell subpopulations and lymphocyte counts in our ongoing clinical trials until we better understand if there is a potential risk in humans. There were no indications of genotoxicity or specific indicators of phototoxicity with beloranib. Embryo-fetal toxicity findings in rats and rabbits have demonstrated significant embryofetal malformations at exposures similar to those achieved in patients. Therefore, female subjects of child bearing potential should take appropriate measures to avoid pregnancy while on treatment.

Based on the safety findings in animals, clinical trials of beloranib have included monitoring for blood cell changes, sperm counts, sperm morphology and hormones in men, as well as frequent pregnancy testing and requirement for redundant, implanted or surgical methods of birth control in women. To date, the clinical findings have shown no evidence of the hematological or male reproductive findings in humans. We believe that, as with other anti-obesity drugs, if approved, beloranib will carry a Category X label and be contraindicated in pregnant women or women looking to become pregnant.

We have initiated a two-year carcinogenicity study in the rat and have recently initiated a six-month transgenic mouse carcinogenicity study. Given that PWS manifests during childhood, preliminary juvenile safety studies have been completed. Following discussions of the pediatric investigational plan with regulatory authorities we are planning to conduct a confirmatory juvenile safety study that will potentially support testing and eventual marketing in the pediatric population.

Future Product Candidates

We have been working since our inception in 2005 to explore and pursue new molecules leveraging the therapeutic effects of MetAP2 inhibitors in metabolic diseases including severe obesity, type 2 diabetes, NAFLD, and NASH. As a direct result of medicinal chemistry efforts oriented to the identification of best in class MetAP2 inhibitors, we have identified compounds of use as potential back-up or follow-on compounds supporting beloranib, as well as novel inhibitors with improved pharmacological and physicochemical features. We continue to explore the utility of these molecules as a component of our program, and have identified a range of candidate molecules being prepared for advancement into early development.

As a part of this effort, we conducted a medicinal chemistry discovery program to find reversible inhibitors of MetAP2 that could be delivered orally and applied broadly across multiple areas of unmet medical need. The

program delivered over 250 molecules in seven molecular families, and ZGN-839 was selected from this collection as a potent inhibitor with drug-like properties. In pre-clinical studies, ZGN-839 lowered body weight by approximately 9% after 16 days of treatment versus control animals and reduced plasma cholesterol and glucose, along with improvements in liver fat and the weight of abdominal adipose tissue in mice that were otherwise obese and insulin resistant due to long-term exposure to a high fat, obesogenic, diet. Further, in a mouse model of NAFLD and NASH, ZGN-839 treatment for four weeks reduced the severity of NAFLD and NASH and reduced plasma glucose. We believe that compounds like ZGN-839 will have utility in the treatment of NAFLD and NASH, and will further cause improvements in cardiovascular risk factors including low density lipoprotein cholesterol.

A synthetic process to produce ZGN-839 for safety testing and clinical trials has been developed. We are currently conducting IND-enabling studies of ZGN-839 and expect to file an IND in the United States in the middle of 2015. Additionally, we are currently evaluating other second-generation MetAP2 inhibitors as potential development candidates for the treatment of severe obesity in the general population.

Manufacturing and Supply

Beloranib is a small molecule drug that is synthesized with readily available raw materials using conventional chemical processes. We previously used a two vial system which will not be used after the ZAF-311 clinical trial. The current process to produce beloranib for clinical trials involves (i) synthesis of crystalline drug substance, (ii) production of sterile crystalline drug substance, (iii) particle size control, formulation and production of sterile active drug product vials, (iv) production of sterile diluent in both prefilled syringes and vials, and (v) production of sterile placebo vials. We control our clinical trial supply chain by periodically meeting to assess clinical trial material needs and status of supply. Clinical trial materials are forecasted on a six month rolling basis taking into account enrollment rates, number of sites, component inventory and clinical kit shelf-life. The clinical supply forecast is maintained internally and used to aid in decision making for cGMP manufacturing as well as clinical kit packaging and labeling. In addition, the CRO we employ maintains an inventory of all clinical kits that are allocated for a clinical study as well as all components needed for the clinical kits. Our internal cross-functional working group discusses inventory on a regular basis. Distribution of kits to clinical sites is controlled via a validated system thus helping to manage inventory at the CRO. Resupply of finished drug product is in progress at our drug product CMO. The manufacturing process is under active development and is not yet validated. Any delays encountered with manufacturing activities, CMO scheduling or raw material supply could delay the manufacturing of finished drug product. Additionally, following commercialization, we plan to establish a convenient dosing form of beloranib to improve the utility, look, convenience and feel of beloranib for patients—for example a pen injector system with single-use disposable cartridges.

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. No long-term supply agreements are in place with our contractors, and each batch is individually contracted under a quality and supply agreement. If we engage new contractors, such contractors must be approved by the FDA and other comparable foreign regulatory agencies. We plan to continue to rely upon contract manufacturers and, potentially, collaboration partners to manufacture commercial quantities of beloranib, if approved. Our current scale of manufacturing is adequate to support all of our needs for clinical trial supplies and launch for orphan markets. For peak usage in orphan markets and for indications with larger populations, we will need to identify contract manufacturers or partners to produce beloranib on a larger scale.

Sales and Marketing

In early 2014, we hired a Chief Commercial Officer, however, given our stage of development, we have not yet established a commercial organization or distribution capabilities, nor have we entered into any partnership or co-promotion arrangements with an established pharmaceutical company. To develop the appropriate

commercial infrastructure to launch beloranib, we may either do so on our own or by establishing alliances with one or more pharmaceutical 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 beloranib 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 beloranib, we will pay single-digit royalties to Children's based on net sales of beloranib 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 beloranib or (ii) 15 years from the date of the agreement. This agreement will remain in effect for the longer of (i) 15 years and (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 beloranib and our other development programs.

Our owned and licensed patents and patent applications relate to beloranib compositions of matter, formulations, polymorphs, methods of treating obesity using dosing regimens of beloranib and methods of treating hypothalamic obesity. The issued U.S. and European patents generally directed to beloranib compositions of matter are exclusively licensed and will each expire in 2019. We own two issued U.S. patents relating to beloranib polymorph compositions of matter that will expire in 2031 and three issued U.S. patents to methods of treating obesity that will expire in 2029. We own pending patent applications in Europe to beloranib polymorph composition of matter and methods of treating obesity that we expect to expire, once issued, in 2031.

As of March 17, 2015, we owned five issued U.S. patents, six pending U.S. patent applications and foreign counterpart applications, and one Patent Cooperation Treaty, or PCT, application that will allow us to seek corresponding protection worldwide, all of which relate to beloranib. We have a license to two U.S. issued patents, one with corresponding issued foreign counterpart patents, that also relate to beloranib. We also co-own one patent application relating to methods of using beloranib.

As of March 17, 2015, we owned nine pending U.S. patent applications with pending foreign counterpart applications and three PCT patent applications, all of which relate to our internal efforts to discover novel MetAP2 inhibitors. Of these, one pending U.S. patent application with pending foreign counterpart patent applications and one PCT patent application relate to our early-stage product candidate ZGN-839.

As of March 17, 2015, we owned one issued patent, two pending U.S. patent applications with pending foreign counterpart patent applications, one pending PCT patent application and two U.S. provisional patent applications that relate to our second-generation injectable MetAP2 inhibitor program.

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 2019 to 2031. 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 beloranib 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.

Obesity Caused by Rare Conditions

There are no current pharmacological treatments for regulating hunger and hyperphagia-related behaviors of patients with PWS and patients with HIAO, and bariatric surgery is contraindicated in patients with PWS and not frequently employed in patients with HIAO. We are aware of a clinical trial that has been completed by Ferring Pharmaceuticals, Inc. to evaluate the use of carbetocin, an analogue of a brain peptide hormone oxytocin hypothesized to increase trust, reduce anxiety and improve behavior in patients with PWS. We also are aware of a clinical trial being conducted by Essentialis, Inc. to evaluate the safety and tolerability of controlled-release diazoxide in patients with PWS and to explore the effects of diazoxide on hyperphagia-related behaviors and energy expenditure. We are aware of an exploratory trial being planned, or in its early phase of execution, by Rhythm Pharmaceuticals, Inc. to evaluate the effect of treatment with RM-493, a melanocortin receptor agonist, in patients with PWS. We are not aware of any clinical trials of drugs specifically targeting patients with HIAO.

Severe Obesity in the General Population

Surgical Approaches

Surgical approaches to treat severe obesity are becoming increasingly accepted and are believed to be the main form of competition to beloranib in this indication. Bariatric surgery, including gastric bypass and gastric banding procedures, is typically employed for obese patients with a BMI exceeding 40 kg/m^2 or those with a BMI greater than 30 kg/m^2 who are experiencing obesity-related complications such as diabetes. However, in December 2010, the FDA's Advisory Committee for Gastroenterology and Urology Devices convened and voted in favor of recommending to the FDA that gastric banding procedures be approved for obese patients with a BMI greater than 30 kg/m^2 who are experiencing obesity related co-morbidities or patients with a BMI greater than 35 kg/m^2 with or without obesity related co-morbidities. Other potential competitors in the severe obesity market include bariatric service providers, and other potential approaches which utilize various implantable devices or surgical tools that have been approved by the FDA, such as EnteroMedics Inc.'s recently FDA-approved (January 2015) VBlock Therapy, or that are in development by companies such as Allergan, Inc., Boston Scientific Corporation, Covidien Ltd., EnteroMedics, Inc., GI Dynamics, Inc., Johnson & Johnson and Medtronic, Inc.

Existing Obesity Drugs

In addition, beloranib will compete with orlistat, lorcaserin, phentermine/topiramate, Contrave and Saxenda, which are approved and currently marketed pharmaceutical products in the United States for the treatment of obesity, and several older agents, indicated for short-term administration, phentermine, phendimetrazine, benzphetamine and diethylpropion. Orlistat is marketed in the United States by the Roche Group under the brand name Xenical and over-the-counter in the United States at half the prescribed dose by GlaxoSmithKline under the brand name alli. In June 2013, Arena Pharmaceuticals, Inc. launched its lorcaserin product, which is marketed in the United States under the name Belviq and in September 2012, Vivus, Inc. commercially launched its combination product, phentermine/topiramate, under the trade name Qsymia. In October 2014 Takeda Pharmaceuticals U.S.A., Inc. and Orexigen Therapeutics, Inc. launched Contrave (naltrexone HCI and bupropion

HCI) extended-release tablets for chronic weight management in obese adults and in December 2014, the FDA approved Novo Nordisk A/S's Saxenda for weight management in obese and overweight patients in the presence of at least one related co-morbid condition.

Despite the large market opportunity for anti-obesity agents, there are relatively few competitive products in late-stage clinical development. Other companies pursuing pharmaceutical treatments for obesity include Neurosearch A/S.

We are not aware of any clinical trials of drugs specifically targeting patients with severe obesity.

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 beloranib. 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 the 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 its implementing 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, warning letters, product recalls or 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 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 pre-clinical laboratory tests, pre-clinical 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;
- Performance of adequate and well-controlled human clinical trials in accordance with applicable IND and other clinical trial-related regulations, sometimes referred to as current good clinical practices, or cGCPs, 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 requirements, or cGMP, 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 pre-clinical 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: pre-clinical and clinical. For new chemical entities, the pre-clinical 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 pre-clinical tests must comply with federal regulations, including GLPs. The sponsor must submit the results of the pre-clinical 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. The central focus of an IND submission is on the general investigational plan and the protocol(s) for human trials. 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 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 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 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 product approval. 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.

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

Progress reports detailing the results of the clinical trials must be submitted at least annually to the FDA and written IND safety reports must be submitted to the FDA and the investigators for serious and unexpected adverse events or any finding from tests in laboratory animals that suggests a significant risk for human subjects. 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 trial may move forward at designated check points based on access to certain data from the 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, 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 trial completion, trial data is analyzed to assess safety and efficacy. The results of pre-clinical 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, purity, potency and efficacy, which is demonstrated by extensive pre-clinical and clinical testing. The application includes both negative or ambiguous results of pre-clinical 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.

In addition, under the Pediatric Research Equity Act, or PREA, 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.

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, effective through September 30, 2015, the user fee for an application requiring clinical data, such as an NDA, is $2,335,200. PDUFA also imposes an annual product fee for human drugs ($104,060) and an annual establishment fee ($554,600) on facilities used to manufacture prescription drugs. 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 NDA and respond to the applicant, and six months from the filing date for a priority 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. In the case of obesity drugs, the FDA normally refers such drugs to the Endocrinologic and Metabolic Drugs Advisory Committee. 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, pre-clinical 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, or withdraw the application. 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 a 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 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 biological 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 European Union 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 meet certain criteria. Specifically, new drugs and biological products are eligible for Fast Track designation if they 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 has the potential to provide safe and

effective therapy where no satisfactory alternative therapy exists or a significant improvement in the treatment, diagnosis or prevention of a disease compared to marketed products. The FDA will attempt to direct additional resources to the evaluation of an application for a new drug or biological product designated for priority review in an effort to facilitate the review. Additionally, a product may be eligible for accelerated approval. 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 other than survival or irreversible morbidity. 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. Fast Track designation, priority review and accelerated approval do not change the standards for approval but may expedite the development or approval process.

Pediatric Trials

Recently, the Food and Drug Administration Safety and Innovation Act, or FDASIA, which was signed into law on July 9, 2012, amended the FDCA. FDASIA 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 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. 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. Submission of a PSP as defined in FDASIA is not required for programs with orphan drug designation.

Post-Marketing Requirements

Following approval of a new product, a pharmaceutical 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"), limitations on industry-sponsored scientific and educational activities, and requirements for promotional activities involving the internet. Although physicians may prescribe legally available drugs for off-label uses, manufacturers may not market or promote such off-label uses. 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.

Prescription drug advertising is subject to federal, state and foreign regulations. In the United States, the FDA regulates prescription drug promotion, including direct-to-consumer advertising. Prescription drug promotional materials must be submitted to the FDA in conjunction with their first use. 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 approved facilities 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, 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, 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 Health Care Reform Law, as amended by the Health Care and Education Affordability Reconciliation Act, 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, 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 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. 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 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 pre-clinical 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 a pediatric trial in accordance with an FDA-issued "Written Request" for such a trial.

European Union Drug Development

In the European Union, 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 pre-clinical and clinical research in the European Union are subject to significant regulatory controls. Although the EU Clinical Trials Directive 2001/20/EC has sought to harmonize the European Union clinical trials regulatory framework, setting out common rules for the control and authorization of clinical trials in the European Union, the European Union 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 European Union countries where the 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.

The European Union clinical trials legislation is currently undergoing a revision process mainly aimed at uniforming and streamlining the clinical trials authorization process, simplifying adverse event reporting procedures, improving the supervision of clinical trials, and increasing their transparency.

European Union Drug Review and Approval

In the European Economic Area, or EEA, (which is comprised of the 27 Member States of the European Union (excluding Croatia) 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 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 European Union.

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 another 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 SPC, 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, SPC, 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 European Union, 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 European Union 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 European Union, 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 European Union 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 European Union would be sufficient to justify the necessary investment in developing the medicinal product.

In the European Union, 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 will be 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 candidate, 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 candidate. 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 Health Care Reform Law, as amended by the Health Care and Education Affordability Reconciliation Act of 2010, or collectively the ACA, enacted in March 2010, is expected to have a significant impact on the health care industry. The ACA is expected 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 is expected to expand and increase industry rebates for drugs covered under Medicaid programs and make changes to the coverage requirements under the Medicare Part D program. We cannot predict the impact of the ACA on pharmaceutical companies as many of the ACA reforms require the promulgation of detailed regulations implementing the statutory provisions which has not yet occurred. For example, 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 by ACA to begin tracking this information in 2013 and to report this information to CMS beginning in 2014.

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, 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 European Union 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 European Union do not follow price structures of the United States and generally tend to be significantly lower.

Employees

As of March 17, 2015, we employed 22 full-time employees, including 15 in research and development and seven in general and administrative, and one part-time employee in general and administrative. We have never had a work stoppage, and none of our employees is represented by a labor organization or 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.

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. We make these reports available through our website as soon as reasonably practicable after we electronically file such reports with, or furnish such reports to, the SEC. You can find, copy and inspect information we file at the SEC's public reference room, which is located at 100 F Street, N.E., Room 1580, Washington, DC 20549. Please call 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 web site 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 on Form 10-K.

ITEM 1A. RISK FACTORS

The following risks and uncertainties, together with all other information in this Annual Report, including our consolidated financial statements and related notes, should be considered carefully. Any of the risk factors we describe below could adversely affect our business, financial condition or results of operations, and could cause the market price of our common stock to fluctuate or decline.

Risks Related to Product Development, Regulatory Approval and Commercialization

We depend almost entirely on the success of one product candidate, beloranib, which is in Phase 3 clinical development for our lead indication of the treatment of obesity and hyperphagia in patients with PWS and Phase 2 clinical development for HIAO and severe obesity in the general population. We cannot be certain that we will be able to obtain regulatory approval for, or successfully commercialize, beloranib.

We currently have only one product candidate, beloranib, in clinical development, and our business depends almost entirely 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. Beloranib, which is currently in Phase 3 clinical development as a treatment for obesity and hyperphagia in Prader-Willi syndrome, or PWS, Phase 2 clinical development for hypothalamic injury-associated obesity, or HIAO, and Phase 2b clinical development for severe obesity in the general population, will require substantial additional clinical development, testing and regulatory approval before we are permitted to commence its commercialization. Our other product candidates, including ZGN-839, are still in pre-clinical development stages. 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 pre-clinical 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 may include post-marketing studies and surveillance, which will require the expenditure of substantial resources beyond the proceeds we currently have on hand. Of the large number of drugs in development in the United States, only a small percentage will successfully complete the U.S. Food and Drug Administration, or FDA, regulatory approval process and is 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 beloranib or any other of our product candidates will be successfully developed or commercialized.

We are not permitted to market beloranib in the United States until we receive approval of a New Drug Application, or an NDA, from the FDA, or in any foreign countries until we receive the requisite approval from such countries. We recently completed three Phase 2 clinical trials of beloranib, one in patients with PWS, one in patients with HIAO and one in severely obese patients. We expect that the FDA will require us to conduct at least one pivotal trial in order to submit an NDA for beloranib as a treatment for patients with PWS. However, meeting the requirements of the FDA or certain European regulatory authorities may require that we conduct additional pivotal trials. We expect that the FDA will also require us to complete our ongoing Phase 2b clinical trial and at least two Phase 3 clinical trials to submit an NDA for beloranib as a treatment for severe obesity in the general population, and may require that we conduct a cardiovascular outcomes trial. Pursuant to the FDA's February 2007 draft guidance to industry on the development of weight management drugs, in order to reasonably estimate the safety of a weight-management drug, Phase 3 clinical trials must randomize approximately 3,000 subjects to active doses of the product and 1,500 subjects to placebo in clinical trials for a one-year duration.

We initiated our Phase 3 clinical program, which is planned to consist of two Phase 3 clinical trials, of beloranib in patients with PWS, with the first Phase 3 trial in the United States having started in September 2014. We plan to initiate our second Phase 3 clinical trial of beloranib in patients with PWS in the European Union in the middle of 2015. We continue to engage in discussions with applicable regulatory authorities to determine if our proposed Phase 3 clinical trials will be sufficient to support an NDA submission to the FDA and a marketing authorization application, or MAA, to the European Medicines Agency, or EMA, and other regulatory agencies seeking approval of beloranib for the treatment of obesity and hyperphagia in patients with PWS. Prior to initiation of our Phase 3 clinical program for beloranib in patients with PWS, we submitted pre-clinical animal studies and clinical trial results for the FDA's review, and have several additional studies to complete, including a human factors study to demonstrate patients' ability to correctly use the device for dispensing beloranib, an abuse potential study and rat and mouse carcinogenicity studies. However, the FDA may require additional pre-clinical animal studies or clinical studies. We also initiated a Phase 2b clinical trial of beloranib as a treatment for severe obesity in the general population in patients who also have type 2 diabetes.

We are also evaluating additional proprietary methionine aminopeptidase 2, or MetAP2, inhibitors beyond beloranib as potential development candidates that would provide increased patient convenience in the form of oral dosing, or an otherwise improved clinical profile. A decision on whether to subsequently advance beloranib into pivotal trials for severe obesity or to leverage the opportunity to advance another MetAP2 inhibitor into early development for severe obesity is anticipated to be made on the basis of results obtained from our Phase 3 clinical trial in the United States of beloranib in patients with PWS and discussions with regulatory authorities.

Accordingly, obtaining approval of an NDA is a complex, lengthy, expensive and uncertain process, and the FDA and certain European regulatory authorities may delay, limit or deny approval of beloranib for many reasons, including, among others:

- we may not be able to demonstrate that beloranib is safe and effective in treating obesity and hyperphagia in patients with PWS, HIAO or severe obesity in the general population, to the satisfaction of the FDA and certain European regulatory authorities;
- the results of our clinical trials may not meet the level of statistical or clinical significance required by the FDA and certain European regulatory authorities for marketing approval;
- the FDA and certain European regulatory authorities may disagree with the number, design, size, duration, conduct or implementation of our clinical trials;
- the FDA and certain European regulatory authorities may require that we conduct additional clinical trials or pre-clinical studies;
- the FDA and certain European regulatory authorities may not approve the formulation, labeling or specifications of beloranib;
- 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 certain European regulatory authorities may find the data from pre-clinical studies and clinical trials insufficient to demonstrate that beloranib's clinical and other benefits outweigh its safety risks;
- the FDA and certain European regulatory authorities may disagree with our interpretation of data from our pre-clinical studies and clinical trials;
- the FDA and certain European regulatory authorities may not accept data generated at our clinical trial sites;
- if and when our NDA is submitted and reviewed by an advisory committee, the FDA may have difficulties scheduling an advisory committee meeting in a timely manner or the advisory committee

may recommend against approval of our application or may recommend that the FDA require, as a condition of approval, additional pre-clinical studies or clinical trials, limitations on approved labeling or distribution and use restrictions;

- the FDA may require development of a Risk Evaluation and Mitigation Strategy, or REMS, as a condition of approval or post-approval;
- the FDA and certain European regulatory authorities may not approve the manufacturing processes or facilities of third-party manufacturers with which we contract; or
- the FDA and certain European regulatory authorities 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 regulatory approval for and successfully market beloranib. Moreover, because our business is almost entirely dependent upon this one product candidate, any such setback in our pursuit of regulatory approval would have a material adverse effect on our business and prospects.

Positive results from early clinical trials of beloranib are not necessarily predictive of the results of later clinical trials of beloranib. If we cannot replicate the positive results from our earlier clinical trials of beloranib in our later-stage clinical trials, we may be unable to successfully develop, obtain regulatory approval for and commercialize beloranib. It may further be necessary to validate different or additional instruments for measuring subjective endpoints, and to show that beloranib has a clinically meaningful impact on those endpoints in order to obtain regulatory approval.

Positive results from our Phase 1 and Phase 2a clinical trials of beloranib may not necessarily be predictive of the results from required later-stage clinical trials. Similarly, even if we are able to complete our Phase 2b or Phase 3 clinical trials of beloranib according to our current development timeline, the positive results from our Phase 1 and Phase 2a clinical trials of beloranib may not be replicated in our Phase 2b or Phase 3 clinical trial results. The design of our Phase 3 clinical program of beloranib as a treatment for obesity and hyperphagia in patients with PWS differs in several aspects from our recently completed Phase 2a clinical trial for PWS. For example, patients with PWS will not be limited to living in closely-controlled PWS-specific group homes like they were in our Phase 2a clinical trial but will be predominantly living in family homes. In addition, patients with PWS will be treated with beloranib for substantially longer than four weeks and our U.S. Phase 3 extension trial, European Phase 3 trial for PWS and all subsequent Phase 2 and 3 studies will test a pre-filled diluent syringe instead of single use glass vials, which were used in our Phase 2a and U.S. Phase 3 clinical trials. One of the Phase 3 clinical trials will be conducted in Europe, where we have not previously conducted clinical trials. Based on discussions with regulatory authorities, the dual primary efficacy endpoints for our Phase 3 clinical trials have changed from improvement in hyperphagia-related behaviors or body fat mass to improvements in hyperphagia-related behaviors or body weight. In our Phase 2a clinical trial for PWS we saw statistically significant improvements in body mass and fat mass; body weight was also reduced, but not to a statistically significant level. In each Phase 3 trial, the trial will be considered successful based on a statistically significant result for either dual primary efficacy endpoint at a p-value of less than 0.025. Later-stage clinical trials will utilize highly rigorous statistical analyses. For example, the results of our Phase 2a clinical trial for severe obesity were based on a per protocol analysis of patients who completed the 12-week dosing in the clinical trial. Later-stage clinical trials will be evaluated based on an intent-to-treat analysis that includes all patients randomized in the clinical trial, regardless of whether they complete treatment, which may lead to different results. The draft statistical analysis plan for our U.S. Phase 3 trial is still under review by the FDA. Moreover, if we fail to validate a caregiver-administered PWS-specific hyperphagia-related behaviors questionnaire, or PWS-HQ, in time for it to be an effective tool to support the data from our Phase 3 clinical trials, our Phase 3 clinical program and, in turn, our regulatory filing may be delayed until we validate the tool or develop and test a new one. This can be a lengthy process.

Many companies in the pharmaceutical and biotechnology industries have suffered significant setbacks in later-stage clinical trials after achieving positive results in early-stage development, and we cannot be certain that

we will not face similar setbacks. These setbacks have been caused by, among other things, pre-clinical findings made while clinical trials were underway or safety or efficacy observations made in clinical trials, including previously unreported adverse events. Moreover, pre-clinical and clinical data are often susceptible to varying interpretations and analyses, and many companies that believed their product candidates performed satisfactorily in pre-clinical studies and clinical trials nonetheless failed to obtain FDA approval. If we fail to produce positive results in our Phase 2b or Phase 3 clinical trials of beloranib, the development timeline and regulatory approval and commercialization prospects for our leading product candidate, and, correspondingly, our business and financial prospects, would be materially adversely affected.

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

We initiated our Phase 3 clinical trial of beloranib as a treatment for obesity and hyperphagia in patients with PWS in the United States in September 2014. We plan to initiate our second Phase 3 trial in the European Union in patients with PWS in the middle of 2015. We also initiated a Phase 2b clinical trial of beloranib as a treatment for severe obesity in the general population in patients who also have type 2 diabetes in December 2014. Despite the guidance received from, and to be received from, these regulatory authorities, both the FDA and the European regulatory authorities can change their positions on the acceptability of our 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, consequently, the ultimate approval and commercial marketing of beloranib. We do not know whether any of these Phase 2b or Phase 3 clinical trials 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 or European regulatory authorities may place an ongoing clinical trial on hold or may deny permission to pursue other clinical trials we want to initiate;
- delays in regulatory filing or receiving regulatory approvals or additional investigational new drug applications, or INDs, that may be required;
- negative results from our ongoing pre-clinical studies, or the FDA or European regulatory authorities may require additional pre-clinical 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, approval to conduct a clinical trial at a prospective site or sites;
- 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 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;
- severe or unexpected drug-related side effects experienced by patients in a clinical trial, including side effects previously identified in our completed clinical trials;
- delays in validating the PWS-HQ or any other self-reported measures of hunger and related endpoints utilized in a clinical trial, including delays caused as a result of the need to translate the PWS-HQ or other self-reported measures of hunger into European languages other than English;

- the FDA or European regulatory authorities may disagree with our clinical trial design and 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;
- reports from pre-clinical or clinical testing of other weight loss therapies that raise safety or efficacy concerns; and
- difficulties retaining patients who have enrolled in a clinical trial but may be prone to withdraw due to rigors of the clinical trials, lack of efficacy, side effects, personal issues or loss of interest.

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, at the sites where the IRBs are overseeing a clinical trial, a data and safety monitoring board, or DSMB, 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 or other regulatory authorities that reveals deficiencies or violations that require us to undertake corrective action, including the imposition of a clinical hold;
- unforeseen safety issues, including any that could be identified in our ongoing pre-clinical 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 certain European regulatory authorities or unanticipated events during our clinical trials of beloranib 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 certain European regulatory authorities or unanticipated events during our clinical trials may force us to adjust our clinical program or the FDA or certain European regulatory authorities may impose additional clinical trial requirements. For instance, the FDA issued draft guidance on developing products for weight management in February 2007, but this guidance may be revised in the near future. In March 2012, the FDA's Endrocrinologic and Metabolic Drugs Advisory Committee met to discuss possible changes to how the FDA evaluates the cardiovascular safety of weight-management drugs. Amendments to our clinical trial protocols would require resubmission to the FDA or certain European regulatory authorities and IRBs 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, the commercial prospects for beloranib 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 beloranib. If these third parties do not successfully carry out their contractual duties or meet expected deadlines, we may not be able to obtain regulatory approval for or commercialize beloranib 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 beloranib and control only 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 trials is conducted in accordance with the applicable protocol, legal, regulatory 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 current Good Clinical Practices, or cGCPs, which are regulations and guidelines 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 cGCP regulations through periodic inspections of clinical trial sponsors, principal investigators and trial sites. If we or our CROs fail to comply with applicable cGCPs, 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 cGCPs. In addition, our clinical trials must be conducted with product produced under current Good Manufacturing Practices, or cGMPs, regulations and will require a large number of test subjects. Our failure or the failure of our CROs 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 do design our clinical trials for beloranib, 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 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 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 beloranib may be delayed or our development program materially and irreversibly harmed. We cannot control the amount and timing of resources these CROs devote to our program or beloranib. If we are unable to rely on clinical data collected by our 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 CROs terminate, we may not be able to enter into arrangements with alternative CROs. If 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 beloranib. As a result, our financial results and the commercial prospects for beloranib in the subject indication would be harmed, our costs could increase and our ability to generate revenue could be delayed.

The number of patients suffering from each of PWS and HIAO is small and has not been established with precision. If the actual number of patients with either of these conditions is smaller than we estimate or if any approval that we obtain is based on a narrower definition of these patient populations, our revenue and ability to achieve profitability 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 or HIAO in any geography. Published population studies estimate that the prevalence of PWS in the United States and in the European Union ranges from 1 in 8,000 to 1 in 50,000. Published population studies estimate that the incidence of craniopharyngioma, the leading cause of HIAO, is 0.13 to 0.17 per 100,000 per year, or approximately 400 to 500 cases per year in the United States and 650 to 850 cases per year in the European Union. The total addressable market opportunity for beloranib for the treatment of patients with PWS or HIAO will ultimately depend upon, among other things, the diagnosis criteria included in the final label for beloranib, if approved for sale for these indications, acceptance by the medical community and patient access, product pricing and reimbursement. If the actual number of patients with PWS or HIAO 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 markets for beloranib for these indications will be smaller than we anticipate.

In addition, we plan to seek approval of beloranib initially for the treatment of adolescent (12 years of age and older) and adult patients with PWS and adolescent and adult patients with HIAO. We believe that approximately 40-50% of patients with PWS are 12 years of age or older. We are currently engaged in early discussions with the FDA and EMA regarding plans for development of beloranib for the treatment of pediatric patients under the age of 12. To support approval for pediatric patients (younger than 12 years of age) we will need to conduct pediatric clinical trials of beloranib for the treatment of these patients with PWS, but we do not yet have plans regarding when these trials will commence. As a result, any FDA approval would likely, at least initially, be limited to use for treating adolescent and adult patients with PWS or adolescent and adult patients with HIAO. This would limit our initial product revenue and may make it more difficult for us to achieve or maintain profitability.

We rely completely on third-party suppliers to manufacture our clinical drug supplies for beloranib, and we intend to rely on third parties to produce commercial supplies of beloranib and pre-clinical, 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 beloranib, or any future product candidates, for use in the conduct of our pre-clinical 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 facilities used by our contract manufacturers, or CMOs, to manufacture the active drug substance, sterile drug substance and final drug product must be approved by the FDA and other comparable foreign regulatory agencies pursuant to inspections that would be conducted after we submit our NDA or relevant foreign regulatory submission to the applicable regulatory agency.

We do not control the manufacturing process of, and are completely dependent on, our CMOs to comply with cGMPs for manufacture of active drug substance, sterile 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. While we manage our quality expectations through a regular 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 the regulatory clearance of our CMOs' facilities generally. If the FDA or an applicable foreign regulatory agency 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 control our clinical trial supply chain by periodically meeting to assess clinical trial material needs and status of supply. Clinical trial materials are forecasted on a six month rolling basis taking into account enrollment rates, number of sites, component inventory and clinical kit shelf-life. The clinical supply forecast is maintained internally and used to aid in decision making for cGMP manufacturing as well as clinical kit packaging and labeling. In addition, the CRO we employ maintains an inventory of all clinical kits that are allocated for a clinical trial as well as all components needed for the clinical kits. Our cross-functional internal working group discusses inventory on a regular basis. Distribution of kits to clinical sites is controlled via a validated system thus helping to manage inventory at the CRO. Resupply of finished drug product is in progress at our drug product CMO. The manufacturing process is under active development and is not yet validated. Any delays encountered with manufacturing activities, CMO scheduling or raw material supply could delay the manufacturing of finished drug product.

We do not have long-term supply agreements in place with our CMOs, and each batch of beloranib is individually contracted under a quality and supply agreement. CMOs are currently supporting clinical activities, however CMOs that will manufacture commercial cGMP batches for beloranib will need to be approved by the FDA and other applicable foreign regulatory agencies, prior to commercialization. We plan to continue to rely upon CMOs and, potentially, collaboration partners to manufacture commercial quantities of beloranib, if approved. Our current scale of manufacturing is adequate to support all of our needs for clinical trial supplies and launch for orphan markets. For peak usage in orphan markets and for indications with larger populations of affected patients, we will need to identify CMOs or partners to produce beloranib on a larger scale.

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

We do not currently have an infrastructure for the sales, marketing and distribution of pharmaceutical products. In order to market beloranib, 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 beloranib in the United States, we may never receive regulatory approval to market beloranib outside of the United States.

We intend to pursue marketing approval of beloranib in the European Union 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 or pre-clinical 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. Marketing approval in one country does not 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 beloranib 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 beloranib, it may not achieve broad market acceptance, which would limit the revenue that we generate from its sales.

The commercial success of beloranib, if approved by the FDA or EMA or other applicable regulatory authorities, will depend upon the awareness and acceptance of beloranib among the medical community, including physicians, patients and healthcare payors. Market acceptance of beloranib, if approved, will depend on a number of factors, including, among others:

- beloranib's demonstrated ability to treat obesity and hyperphagia in patients with PWS, HIAO, or severe obesity in the general population and, if required by any applicable regulatory authority in connection with the approval for these indications, to provide patients with incremental health benefits, as compared with other available weight loss therapies, devices or surgeries;
- the relative convenience and ease of subcutaneous injections as the necessary method of administration of beloranib, including as compared with other treatments for severely obese patients;
- the prevalence and severity of any adverse side effects associated with beloranib, such as nausea, vomiting, headaches and difficulty sleeping or falling asleep;
- limitations or warnings contained in the labeling approved for beloranib by the FDA, EMA, or other regulatory authorities;
- availability of alternative treatments, including a number of competitive obesity therapies already approved or expected to be commercially launched in the near future;
- 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 and cost effectiveness;
- the effectiveness of our sales and marketing strategies;
- our ability to increase awareness of beloranib through marketing efforts;
- our ability to obtain sufficient third-party coverage or reimbursement; and
- the willingness of patients to pay out-of-pocket in the absence of third-party coverage.

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

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 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. In our recently completed Phase 2 clinical trials of beloranib, the main adverse events, or AEs, including those leading to premature treatment discontinuation, in patients dosed with beloranib, have been sleep disturbances, principally manifested as delayed onset of sleep, as well as nausea and vomiting.

The safety data we have disclosed to date represents our interpretation of the data at the time of disclosure and it is subject to our further review and analysis. There have been no serious adverse events, or SAEs, attributed to beloranib in our completed clinical trials. However, SAEs that are not characterized by clinical investigators as possibly related to beloranib or SAEs that occur in small numbers may not be disclosed to the public until such time the various documents submitted to the FDA as part of the approval process are made public. We are unable to determine if the subsequent disclosure of SAEs will have an adverse effect on our stock price. In addition, our interpretation of the safety data from our clinical trials is contingent upon the review and ultimate approval of the FDA or other regulatory authorities. The FDA or other regulatory authorities may not agree with our methods of analysis or our interpretation of the results.

Further, if beloranib receives 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 withdraw or limit their approval of the product;
- regulatory authorities may require the addition of labeling statements, such as a “boxed” warning or a contraindication;
- 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 products 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.

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

Even if we receive marketing approval for beloranib, regulatory authorities may still impose significant restrictions on beloranib’s indicated uses or marketing or impose ongoing requirements for potentially costly post-approval studies. Beloranib 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.

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 beloranib, such as adverse events of unanticipated severity or frequency, or problems with the facility where beloranib is manufactured, a regulatory agency may impose restrictions on beloranib, the manufacturer or us, including requiring withdrawal of beloranib from the market or suspension of manufacturing. If we or the manufacturing facilities for beloranib 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 beloranib.

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 beloranib 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 beloranib. 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.

There are no current pharmacological treatments for regulating hunger and hyperphagia-related behaviors of patients with PWS or patients with HIAO, and bariatric surgery is contraindicated in patients with PWS and is not frequently employed in patients with HIAO. We are aware of a clinical trial that was recently completed by Ferring Pharmaceuticals, Inc. to evaluate the use of carbetocin, an analogue of a brain peptide hormone oxytocin hypothesized to increase trust, reduce anxiety and improve behavior in patients with PWS. We also are aware of a clinical trial being conducted by Essentialis, Inc. to evaluate the safety and tolerability of controlled-release diazoxide in patients with PWS and to explore the effects of diazoxide on hyperphagia-related behaviors and energy expenditure. We are aware of an exploratory trial being planned, or in its early phase of execution, by Rhythm Pharmaceuticals, Inc. to evaluate the effect of treatment with RM-493, a melanocortin receptor agonist, in patients with PWS. In addition, any of our competitors may develop a drug to treat patients with PWS at any time. We are not aware of any clinical trials of drugs specifically targeting patients with HIAO.

Other potential competitors in the severe obesity market include bariatric service providers, and other potential approaches which utilize various implantable devices or surgical tools that have been approved by the FDA, such as EnteroMedics Inc.'s recently FDA-approved (January 2015) VBlock Therapy, or that are in development by companies such as Allergan, Inc., Boston Scientific Corporation, Covidien Ltd., GI Dynamics, Inc., Johnson & Johnson and Medtronic, Inc. In addition, beloranib will compete with orlistat, phentermine/topiramate and lorcaserin, approved and currently marketed pharmaceutical products in the United States for the treatment of obesity, and several older agents, indicated for short-term administration, including phentermine, phendimetrazine, benzphetamine and diethylpropion. Orlistat is marketed in the United States by the Roche Group under the brand name Xenical and over-the-counter in the United States at half the prescribed dose by GlaxoSmithKline under the brand name alli. In June 2013, Arena Pharmaceuticals, Inc. launched its lorcaserin product, which is marketed in the United States under the name Belviq and in September 2012, Vivus, Inc. commercially launched its combination product, phentermine/topiramate, under the trade name Qsymia. In October 2014 Takeda Pharmaceuticals U.S.A., Inc. and Orexigen Therapeutics, Inc. launched Contrave (naltrexone HCI and bupropion HCI) extended-release tablets for chronic weight management in obese adults and in December 2014 the FDA approved Novo Nordisk A/S's Saxenda for weight management in obese and overweight patients in the presence of at least one related co-morbid condition. Neurosearch A/S is also pursuing pharmaceutical treatments for obesity.

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 beloranib in foreign markets for which we may rely on collaborations with third parties. If we commercialize beloranib in foreign markets, we would be subject to additional risks and uncertainties, including:

- our customers' ability to obtain reimbursement for beloranib 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 beloranib 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, 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 beloranib, 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 beloranib, if we obtain marketing approval. Restrictions under applicable federal and state healthcare laws and regulations include the following:

- The federal healthcare anti-kickback statute prohibits, among other things, persons from knowingly and willfully soliciting, offering, receiving or providing 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 Act imposes criminal and civil penalties, including those from civil whistleblower or qui tam actions, 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, 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.
- 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.

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 beloranib, if approved. In particular, a product may not be promoted for uses that are not approved by the FDA or such other regulatory agencies as reflected in the product's approved labeling. If we receive marketing approval for beloranib as a treatment for obesity and hyperphagia in patients with PWS or patients with HIAO physicians may nevertheless prescribe beloranib 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. 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 beloranib, 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 beloranib.

Market acceptance and sales of beloranib 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

beloranib and, if reimbursement is available, the level of such reimbursement. Reimbursement may impact the demand for, or the price of, beloranib. If reimbursement is not available or is available only at limited levels, we may not be able to successfully commercialize beloranib.

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 beloranib with other available therapies. If reimbursement for beloranib 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.

Even though we have received orphan drug designation for PWS, we may not receive orphan drug exclusivity for beloranib.

As part of our business strategy, we have obtained orphan drug designation in the United States and the European Union for beloranib for the treatment of patients with PWS. 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. To obtain orphan drug exclusivity for a drug that shares the same active chemical entity as an already orphan designated drug, it must be demonstrated to the FDA that the drug is safer or more effective than the approved orphan designated drug, or that it makes a major contribution to patient care. In addition, 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. In addition, orphan drug exclusive marketing rights in the United States may be lost if the FDA later determines that the request for designation was materially defective or if the manufacturer is unable to assure sufficient quantity of the drug to meet the needs of patients with the rare disease or condition or if another drug with the same active moiety is determined to be safer, more effective, or represents a major contribution to patient care.

In the European Union, orphan drug designation also entitles a party to financial incentives such as reduction of fees or fee waivers. In addition, ten years of market exclusivity is granted following drug product approval, meaning that another application for marketing authorization of a later similar medicinal product for the same therapeutic indication will generally not be approved in the European Union. 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 to not justify maintenance of market exclusivity.

Our product development programs for candidates other than beloranib may require substantial financial resources and may ultimately be unsuccessful.

In addition to the development of beloranib, we may pursue development of our other early-stage development programs. None of our other potential product candidates has commenced any clinical trials, and there are a number of FDA and certain European regulatory requirements that we must satisfy before we can commence clinical trials. Satisfaction of these requirements will entail substantial time, effort and financial resources. We may never satisfy these requirements. 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 beloranib, 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 Relating to Our Intellectual Property Rights

If we are unable to adequately protect our proprietary technology or maintain issued patents which are sufficient to protect beloranib, 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.

Our owned and licensed patents and patent applications relate to beloranib compositions of matter, formulations, polymorphs, methods of treating obesity using dosing regimens of beloranib, and methods of treating hypothalamic obesity. The issued U.S. and European patents generally directed to beloranib compositions of matter are exclusively licensed and will each expire in 2019. We own two issued U.S. patents relating to beloranib polymorph compositions of matter that will expire in 2031 and two issued U.S. patents to methods of treating obesity that will expire in 2029. We own pending patent applications in Europe to beloranib polymorph composition of matter and methods of treating obesity that we expect to expire, once issued, in 2031.

As of March 17, 2015, we owned five issued U.S. patents, six pending U.S. patent applications and foreign counterpart applications, and one Patent Cooperation Treaty, or PCT, application that will allow us to seek corresponding protection worldwide, all of which relate to beloranib. We have a license to two U.S. issued patents, one with corresponding issued foreign counterpart patents, that also relate to beloranib. We also co-own one patent application relating to methods of using beloranib.

As of March 17, 2015, we owned nine pending U.S. patent applications with pending foreign counterpart applications and three PCT patent applications, all of which relate to our internal efforts to discover novel MetAP2 inhibitors. Of these, one pending U.S. patent application with pending foreign counterpart patent applications and one PCT patent application relate to our early-stage product candidate ZGN-839.

As of March 17, 2015, we owned one issued U.S. patent, two pending U.S. patent applications with pending foreign counterpart patent applications, one pending PCT patent application and two U.S. provisional patent applications that relate to our second-generation injectable MetAP2 inhibitor program.

We cannot provide any assurances that any of our patents have, or that any of our pending patent applications that mature into issued patents will include, claims with a scope sufficient to protect beloranib or 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 beloranib.

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. We may not be able to prevent the unauthorized disclosure or use of our technical knowledge or trade secrets by consultants, vendors, former employees and current employees. 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 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 beloranib 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 beloranib, 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 beloranib or any other products or product candidates;
- any of our pending patent applications will issue as patents;
- we will be able to successfully commercialize beloranib, 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 beloranib, 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 beloranib 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 attorney's 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 beloranib.

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 beloranib;
- 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, beloranib 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. 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. If we were to lose our rights to licensed intellectual property, we may not be able to continue developing or commercializing beloranib or our other product candidates, if approved.

We have licensed our rights to beloranib from Chong Kun Dang Pharmaceutical Corp. of South Korea, or CKD. Our license with CKD imposes various obligations on us, including a requirement to use commercially reasonable efforts to develop beloranib and provides CKD the right to terminate the license thereunder in the event of a material breach. For example, CKD may allege that we have breached our license agreement and may accordingly seek to terminate our license with them. Termination of our license from CKD 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 beloranib, if approved, as well as harm our competitive business position and our business prospects. We also have an exclusive license with Children's Medical Center Corporation, or Children's, pursuant to which we exclusively licensed certain patient rights relating to decreasing the growth of fat tissue from Children's on a worldwide basis.

We may enter into additional license(s) to third-party intellectual property that are necessary or useful to our business. Future licensor(s) may also allege that we have breached our license agreement and may accordingly seek to terminate our license with them. In addition, future licensor(s) 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 beloranib and failure to secure such registrations could adversely affect our business.

We have not yet registered trademarks for a commercial trade name for beloranib. 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 beloranib, our business may be materially harmed.

Depending upon the timing, duration and specifics of FDA marketing approval of beloranib, one or more of the U.S. patents we license 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.

The United States has recently enacted and is currently implementing the America Invents Act of 2011, which is wide-ranging patent reform legislation. Further, 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. In addition to increasing uncertainty with regard to our ability to obtain future patents, this combination of events has created uncertainty with respect to the value of

patents, once obtained. Depending on decisions by the U.S. Congress, the federal courts and the U.S. PTO, 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 or future patents.

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 commercialize beloranib, which would materially adversely affect our commercial development efforts.

General Company-Related Risks

We will need to develop and expand our company, and we may encounter difficulties in managing this development and expansion, which could disrupt our operations.

As of March 17, 2015, we had 22 full-time employees and one part-time employee, and as we advance beloranib into later-stage clinical trials, we expect to increase our number of employees and the scope of our operations. To manage our anticipated development and expansion, we must continue to implement and improve our managerial, operational and financial systems, expand our facilities and continue to recruit and train additional qualified personnel. Also, our management may need to divert a disproportionate amount of its attention away from its day-to-day activities and devote a substantial amount of time to managing these development activities. Due to our limited resources, we may not be able to effectively manage the expansion of our operations or recruit and train additional qualified personnel. This may result in weaknesses in our infrastructure, give rise to operational mistakes, loss of business opportunities, loss of employees and reduced productivity among remaining employees. The physical expansion of our operations may lead to significant costs and may divert financial resources from other projects, such as the development of beloranib. If our management is unable to effectively manage our expected development and expansion, our expenses may increase more than expected, our ability to generate or increase our revenue could be reduced and we may not be able to implement our business strategy. Our future financial performance and our ability to commercialize beloranib, if approved, and compete effectively will depend, in part, on our ability to effectively manage the future development and expansion of our company.

Our future success depends on our ability to retain our Chief Executive Officer, and to attract, retain and motivate qualified personnel.

We are highly dependent on Dr. Thomas E. Hughes, our Chief Executive Officer. We have entered into an employment agreement with Dr. Hughes, but he may terminate his employment with us at any time. Although we do not have any reason to believe that we will lose the services of Dr. Hughes in the foreseeable future, the loss of his services might impede the achievement of our research, development and commercialization objectives. We also do not have any key-man life insurance on Dr. Hughes. We 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 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 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 beloranib in clinical trials and the sale of beloranib, if 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 beloranib. For example, we may be sued if any product we develop allegedly causes injury 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 beloranib or any future 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 beloranib or any future 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 beloranib, 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 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. We anticipate being first required to issue management's annual report on internal control over financial reporting, pursuant to Section 404 of the Sarbanes-Oxley Act, in connection with issuing our consolidated financial statements as of and for the year ending December 31, 2015.

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 will be applicable to us as a public company. If we fail to staff our accounting and finance function 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.

In order to satisfy our obligations as a public company, we will need to hire additional qualified accounting and financial personnel with appropriate public company experience.

As a newly public company, we will need to establish and maintain effective disclosure and financial controls and make changes in our corporate governance practices. We will need to hire additional accounting and financial personnel with appropriate public company experience and technical accounting knowledge, and it may be difficult to recruit and maintain such personnel. Even if we are able to hire appropriate personnel, our existing operating expenses and operations will be impacted by the direct costs of their employment and the indirect consequences related to the diversion of management resources from product development efforts.

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

As of December 31, 2014, we had federal and state net operating loss carryforwards of $17.0 million and $9.6 million, respectively. Our federal net operating loss carryforwards begin to expire in 2026 and our state net

operating loss carryforwards begin to expire in 2030. As of December 31, 2014, we also had federal and state research and development tax credit carryforwards of $7.7 million and $1.9 million, respectively, which begin to expire in 2026 and 2021, respectively. Under Section 382 of the Internal Revenue Code of 1986, as amended, or the Code, changes in our ownership may limit the amount of our net operating loss carryforwards and research and development 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 research and development tax credit carryforwards before they expire. Our recent follow-on public offering, 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 recent 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.

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. The recent global financial crisis caused extreme volatility and disruptions in the capital and credit markets. A severe or prolonged economic downturn, such as the recent global financial crisis, 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 beloranib 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, accident, or security breach to date, 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 beloranib 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 beloranib 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 weight loss platform. Although beloranib is currently in clinical development, 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 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 beloranib and ZGN-839. We have never generated any revenue from product sales. We have not obtained regulatory approvals for any of our product candidates.

Since our inception, we have focused substantially all of our efforts and financial resources on developing beloranib, which is currently 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 HIAO and severe obesity in the general population. 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 offering, and have incurred losses in each year since our inception. Our net losses were $36.5 million for the year ended December 31, 2014. As of December 31, 2014, we had a deficit accumulated of $105.4 million. Substantially all of our operating losses resulted from costs incurred in connection with our development programs for beloranib and ZGN-839, 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' deficit and working capital. We expect our research and development expenses to significantly increase in connection with our additional clinical trials of beloranib and development of ZGN-839 and of any other product candidates we may choose to pursue. In addition, if we obtain marketing approval for beloranib, we will incur significant sales, marketing and outsourced manufacturing expenses. Now that we are a public company, we will incur additional costs associated with operating as a public company. As a result, we expect to continue to incur significant and increasing operating losses 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 our lead product candidate, beloranib, 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, beloranib. Our ability to generate revenue depends on a number of factors, including, but not limited to, our ability to:

- initiate and successfully complete later-stage clinical trials that meet their clinical endpoints;
- initiate and successfully complete all safety studies required to obtain U.S. and foreign marketing approval for beloranib in the indications we are pursuing;
- commercialize beloranib, if approved, by developing a sales force or entering into collaborations with third parties; and
- achieve market acceptance of beloranib 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 as we prepare to commercialize beloranib. Even if we initiate and successfully complete our pivotal clinical trials of beloranib, and beloranib is approved for commercial sale, and despite expending these costs, beloranib may not be a commercially successful drug. 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.

We are currently advancing beloranib through clinical development. 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 beloranib in later-stage, more costly clinical trials. Depending on the status of regulatory approval or, if approved, commercialization of beloranib, as well as the progress we make in selling beloranib, we may 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 beloranib or otherwise expand more rapidly than we presently anticipate.

As of December 31, 2014, our cash and cash equivalents and marketable securities were $115.5 million. We also completed our follow-on public offering on January 28, 2015, which raised net proceeds of approximately $129.5 million, based on the public offering price of $35.00 per share, after deducting underwriting discounts and commissions, and estimated offering expenses. We expect that the net proceeds from the follow-on public offering, together with our cash and cash equivalents prior to the follow-on public offering, will be sufficient to fund our current operations for at least the next 18 months. 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. To the extent that we raise additional capital through the sale of common stock or securities convertible or exchangeable into common stock, your 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 your rights as a stockholder. 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 beloranib, 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 may fluctuate significantly.

Our IPO was completed on June 24, 2014 at a price of $16.00 per share and our follow-on public offering was completed on January 28, 2015 at a price of $35.00 per share. A public market for our common stock has only been in existence for a short period of time. An active public market for our common stock may not develop or be sustained.

In addition, the market price of shares of our common stock could 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 pre-clinical studies and clinical trials of beloranib;
- the failure of the FDA or the EMA to approve beloranib;
- announcements of new products, technologies, commercial relationships, acquisitions or other events by us or our competitors;
- the success or failure of other weight loss therapies;
- regulatory or legal developments in the United States and other countries;
- failure of beloranib, if approved, to achieve commercial success;
- 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. If any of our stockholders brought a lawsuit against us, we could incur substantial costs defending the lawsuit. Such a lawsuit could also divert the time and attention of our management.

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

As of March 17, 2015, the existing holdings of our executive officers, directors, principal stockholders and their affiliates, including investment funds affiliated with Atlas Ventures, or Atlas, investment funds affiliated with Third Rock Ventures, or TRV, investment funds affiliated with Alta Partners, or Alta, and entities affiliated with Fidelity Investment, or Fidelity, represent beneficial ownership, in the aggregate, of approximately 62.3% 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 will have broad discretion in how we use the proceeds of our IPO and our follow-on public offering. We may not use these proceeds effectively, which could affect our results of operations and cause our stock price to decline.

We will have considerable discretion in the application of the net proceeds of our IPO and our follow-on public offering. We intend to use the net proceeds to advance the clinical development of beloranib as a treatment for obesity and hyperphagia in PWS patients and HIAO, to develop multiple back-up molecules of beloranib as a treatment for severe obesity in the general population, to continue the development and initiate clinical development of ZGN-839, to develop a pen-injector system for eventual commercial use in PWS, HIAO and severe obesity in the general population and to fund new and ongoing research and development activities, working capital and other general corporate purposes, which may include funding for the hiring of additional personnel, capital expenditures, early commercialization activities and the costs of operating as a public company. As a result, investors will be relying upon management's judgment with only limited information about our specific intentions for the use of the balance of the net proceeds. We may use the net proceeds for purposes that do not yield a significant return or any return at all for our stockholders. In addition, pending their use, we may invest the net proceeds in a manner that does not produce income or that loses value.

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. If we were to be sued, it could result in substantial costs and a diversion of management's attention and resources, which could harm our business.

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

We 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, 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 $1.0 billion or more; (ii) the last day of our fiscal year following the fifth anniversary of the date of the completion of our IPO; (iii) the date on which we have issued more than $1.0 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 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 your sole source of gain for the foreseeable future. Consequently, in the foreseeable future, you will likely only experience a gain from your investment in our common stock if the price of our common stock increases.

If equity research analysts do not 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 5,952 square feet of office space at 175 Portland Street, 4th Floor, Boston, Massachusetts from May 15, 2014 to July 31, 2017, with an option to extend for three additional years. We believe that our existing facilities are adequate for our current needs. When our lease expires, we may renew the existing lease 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 priced at $16.00 per share on June 18, 2014. The following table sets forth on a per share basis, for the periods indicated, the low and high prices of our common stock as reported by the NASDAQ Global Market for our fiscal year ended December 31, 2014 since our initial public offering.

	High	Low
2014		
Second Quarter (from June 19, 2014)	$21.01	$19.23
Third Quarter	$21.96	$17.06
Fourth Quarter	$32.25	$16.01

On March 17, 2015, the last reported sales price of our common stock on the Nasdaq Global Market was $45.57 and as of March 17, 2015, there were approximately 27 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.

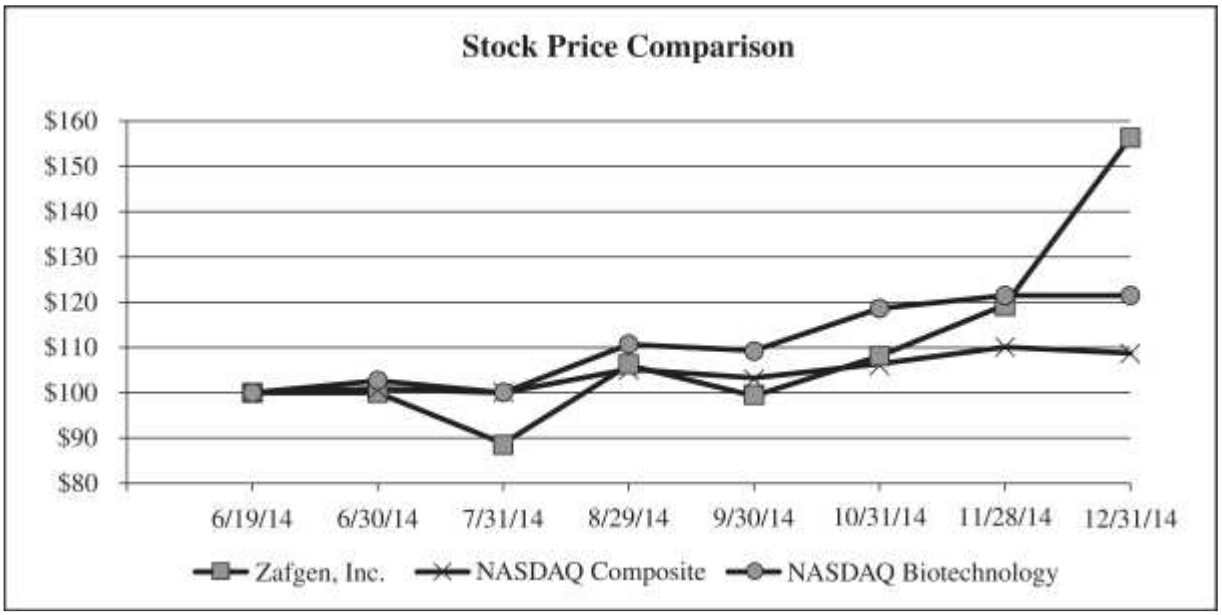
Dividend Policy

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.

Stock Performance Graph

This graph is not "soliciting material," is not deemed "filed" with the SEC and is not to be incorporated by reference into any of our filings under the Securities Act of 1933, as amended, or the Securities Exchange Act of 1934, as amended, whether made before or after the date hereof and irrespective of any general incorporation language in any such filing.

The following graph shows the total stockholder return of an investment of $100 in cash on June 19, 2014 (the first day of trading of our common stock), through December 31, 2014 for (i) our common stock, (ii) the NASDAQ Composite Index and (iii) the NASDAQ Biotechnology Index. Pursuant to applicable Securities and Exchange Commission rules, all values assume reinvestment of the full amount of all dividends, however no dividends have been declared on our common stock to date. The stockholder return shown on the graph below is not necessarily indicative of future performance, and we do not make or endorse any predictions as to future stockholder returns.



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."

Sales of Unregistered Securities

On February 28, 2014, we issued an aggregate of 204,101 shares of Series E redeemable convertible preferred stock to four investors for aggregate consideration of $443,409 in cash.

On November 20, 2014, we issued an aggregate of 171,750 shares of common stock to one of our collaborators in lieu of a cash payment of $3,250,000 in milestone payments.

No underwriters were used in the foregoing transactions. All sales of securities described above were made in reliance upon the exemption from registration provided by Section 4(2) of the Securities Act (and/or Regulation D promulgated thereunder) for transactions by an issuer not involving a public offering. All of the foregoing securities are deemed restricted securities for the purposes of the Securities Act.

Upon the closing of our IPO, all of the outstanding shares of our convertible preferred stock were converted into 15,077,621 shares of common stock. The shares of common stock issued pursuant to such conversion were issued in reliance on the exemption from registration provided by Section 3(a)(9) of the Securities Act, which exemption is available for transactions involving securities exchanged by the issuer with its existing security holders exclusively where no commission or other remuneration is paid or given directly or indirectly for soliciting such exchange.

From January 1, 2014 through June 19, 2014, we granted stock options to purchase an aggregate of 529,555 shares of our common stock, with exercise prices ranging from $9.67 to $16.00 per share, to employees, directors and consultants pursuant to our stock option plan. The issuances of these securities were exempt either pursuant to Rule 701, as a transaction pursuant to a compensatory benefit plan, or pursuant to Section 4(2), as a transaction by an issuer not involving a public offering.

Use of Proceeds

On June 24, 2014, we closed the sale of 6,900,000 shares of common stock to the public (inclusive of 900,000 shares of common stock sold by us pursuant to the full exercise of an overallotment option granted to the underwriters) at a price of $16.00 per share, before underwriting discounts. The offer and sale of the shares in our IPO was registered under the Securities Act pursuant to registration statements on Form S-1 (File No. 377-00464), which was filed with the SEC on January 31, 2014 and amended subsequently and declared effective by the SEC on June 18, 2014, and Form S-1MEF (File No. 333-196891), which was filed with the SEC on June 18, 2014 and automatically effective upon filing. There has been no change in the use of proceeds from our IPO.

Issuer Purchases of Equity Securities by the Issuer and Affiliated Purchasers

None.

ITEM 6. SELECTED FINANCIAL DATA

The selected financial data set forth below as of December 31, 2014 and 2013 and for each of the years ended December 31, 2014, 2013 and 2012, has been derived from the audited consolidated financial statements of the Company, which are included elsewhere in this Annual Report on Form 10-K. The selected financial data as of December 31, 2012 and 2011 and for each of the years then ended has been derived from the audited consolidated financial statements not included in this Annual Report on Form 10-K. 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,			
	2014	2013	2012	2011
	(in thousands, except per share data)			
Statement of Operations Data:				
Revenue	$ —	$ —	$ —	$ —
Operating expenses:				
Research and development	27,391	9,561	11,544	11,403
General and administrative	8,141	4,219	2,247	1,751
Total operating expenses	35,532	13,780	13,791	13,154
Loss from operations	(35,532)	(13,780)	(13,791)	(13,154)
Other income (expense):				
Interest income	28	—	—	—
Interest expense	(870)	—	(97)	—
Foreign currency transaction gains (losses), net	(104)	(247)	8	(3)
Total other income (expense), net	(946)	(247)	(89)	(3)
Net loss	(36,478)	(14,027)	(13,880)	(13,157)
Accretion of redeemable convertible preferred stock to redemption value	(92)	(213)	(67)	(53)
Net loss attributable to common stockholders	$ (36,570)	$ (14,240)	$(13,947)	$(13,210)
Net loss per share attributable to common stockholders, basic and diluted(1)	$ (3.00)	$ (19.53)	$ (19.65)	$ (19.17)
Weighted average common shares outstanding, basic and diluted	12,189	729	710	689

	December 31,			
	2014	2013	2012	2011
		(in thousands)		
Balance Sheet Data:				
Cash and cash equivalents and marketable securities	$115,462	$ 35,517	$ 9,935	$ 1,467
Working capital (2)	110,297	34,443	7,394	(414)
Total assets	117,519	38,138	10,986	1,628
Notes payable, net of discount, long term	6,177	—	—	—
Redeemable convertible preferred stock	—	103,797	62,785	40,575
Total stockholders' equity (deficit)	104,441	(68,574)	(54,729)	(40,916)

(1) See Note 10 to our audited 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 together 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. This discussion contains forward-looking statements that involve risks and uncertainties. Our actual results could differ materially from those described in, or implied by, the 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."

Overview

We are a biopharmaceutical company dedicated to significantly improving the health and well-being of patients affected by obesity and complex metabolic disorders. Beloranib, our lead product candidate, is a novel, first-in-class, twice-weekly subcutaneous injection being developed for the treatment of multiple indications, including severe obesity in two rare diseases, Prader-Willi syndrome, or PWS, and hypothalamic injury-associated obesity, or HIAO, including craniopharyngioma-associated obesity; and severe obesity in the general population.

Obesity is a complex medical disorder involving appetite dysregulation and altered lipid and energy metabolism that results in excessive accumulation of fat tissue. Weight loss and hunger control are urgently needed for certain subpopulations of obese patients, in which obesity is life-threatening and a co-morbidity of an underlying condition such as PWS and HIAO that, while rare, occurs most commonly as a consequence of treatment for craniopharyngioma and other mid-brain tumors. PWS and HIAO are characterized by uncontrollable hunger resulting from damage to or impaired functioning of the hypothalamus, an area of the brain responsible for many functions including the neurophysiological drive to eat.

Since our inception in November 2005, we have devoted substantially all of our resources to developing beloranib and ZGN-839, building our intellectual property portfolio, developing our supply chain, business planning, raising capital, and providing general and administrative support for these operations. Prior to our initial public offering, or 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. From our inception through December 31, 2014, we have received gross proceeds of $104.0 million from such transactions. During 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.

On January 28, 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 approximately $129.5 million based upon the price of $35.00 per share and after deducting underwriting discounts and commissions, and estimated offering expenses.

We have never generated any revenue and have incurred net losses in each year since our inception. We have an accumulated deficit of $105.4 million as of December 31, 2014. Our net loss was $36.5 million, $14.0 million and $13.9 million for the years ended December 31, 2014, 2013 and 2012, respectively. These losses have resulted principally from costs incurred in connection with in-licensing our product candidates, research and development activities and general and administrative costs associated with our operations. We expect to incur significant expenses and increasing operating losses for the foreseeable future.

We expect that our expenses will increase substantially in connection with our ongoing activities, as we:

- advance the clinical development of beloranib as a treatment for obesity and hyperphagia in patients with PWS through our Phase 3 clinical trials;
- advance the clinical development of beloranib as a treatment for patients with HIAO;
- initiate Investigational New Drug Application, or IND, enabling studies and clinical development of ZGN-839 and our second-generation MetAP2 inhibitors;
- advance the clinical development of beloranib as a treatment for severe obesity in the general population through a Phase 2b clinical trial;
- seek to identify additional indications for beloranib;
- 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 or private equity or 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 and cash equivalents and marketable securities as of December 31, 2014, together with the net proceeds of our follow-on offering completed in January 2015, will enable us to fund our operating expenses and capital expenditure requirements for at least the next 18 months. 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.

Operating Expenses

The majority of our operating expenses since inception have consisted primarily of in-licensing costs of our product candidate beloranib, 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, pre-clinical studies and clinical trial activities;
- external costs of outside consultants;
- payments made under our third-party licensing agreements;
- laboratory consumables; and
- allocated facility-related costs.

We have been developing beloranib, ZGN-839, and our second-generation MetAP2 inhibitors, and typically use our employee, consultant and infrastructure resources across our 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.

The following table summarizes our research and development expenses by program:

	Year Ended December 31,		
	2014	2013	2012
		(in thousands)	
Beloranib	$19,738	$5,881	$ 6,952
ZGN-839 and other early stage development activities	1,562	295	2,193
Unallocated expenses	6,091	3,385	2,399
Total research and development expenses	$27,391	$9,561	$11,544

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 continue to increase in the foreseeable future as we pursue later stages of 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 our ongoing as well as any additional clinical trials and other research and development activities;
- future 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 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, 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.

We expect that general and administrative expenses will increase in the future as we expand our operating activities and incur additional costs associated with operating as a public company. These public company related increases will likely include additional costs related to personnel; legal, accounting and audit services; directors' and officers' liability insurance premiums; and investor relations. In addition, if we obtain marketing approval for beloranib, we will incur significant sales and marketing expenses.

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 increase in the future due to increased invested balances from cash proceeds received from our IPO in June 2014 and the follow-on offering that we closed in January 2015.

Interest expense. Interest expense consisted of interest expense on our outstanding convertible promissory notes at the stated interest rates and interest expense related to the amortization of deferred financing costs associated with our issuances of the convertible promissory notes. As of December 31, 2012, all of our outstanding convertible promissory notes and accrued interest had been converted into shares of our redeemable convertible preferred stock. As a result, we no longer incur interest expense related to this debt. Since March 2014, we have recorded interest expense for outstanding borrowings under a credit facility that we entered into on March 31, 2014, consisting of the stated interest of 8.1% per year due on outstanding borrowings, a final payment of 6% of amounts drawn down that is being 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 discount relating to the credit facility, and a fee which was due to the lender upon the completion of our IPO.

Foreign currency transaction gains (losses), net. Foreign currency transaction gains (losses), 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 research and development tax credits, due to our uncertainty of realizing a benefit from those items. As of December 31, 2014, we had federal and state net operating loss carryforwards of $17.0 million and $9.6 million, respectively. Our federal net operating loss carryforwards begin to expire in 2026 and our state net operating carryforwards begin to expire in 2030. We also had federal and state research and development tax credit carryforwards of $7.7 million and $1.9 million, respectively, as of December 31, 2014, which begin to expire in 2026 and 2021, respectively.

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 on Form 10-K for information about these critical accounting policies as well as a description of our other significant accounting policies.

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.

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 pre-clinical 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, pre-clinical 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, net of estimated forfeitures, 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.

We estimate the fair value of each stock option grant using the Black-Scholes option-pricing model, which uses as inputs the fair value of our common stock and assumptions we make for the volatility of our common stock, the expected term of our stock options, the risk-free interest rate for a period that approximates the expected term of our stock options and our expected dividend yield. Until completion of our IPO in June 2014, we were a private company and lacked company-specific historical and implied volatility information. Therefore, we estimated our expected volatility based on the historical volatility of our publicly traded peer companies and expect to continue to do so until such time as we have adequate historical data regarding the volatility of our traded stock price. The expected term of our options has been determined utilizing the “simplified” method for awards that qualify as “plain-vanilla” options, while the expected term of our options granted to consultants and nonemployees has been determined based on the contractual term of the 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 we have never paid cash dividends and do not expect to pay any cash dividends in the foreseeable future.

The assumptions we used to determine the fair value of stock options granted to employees and directors are as follows, presented on a weighted average basis (we did not grant any stock options to employees or directors during the year ended December 31, 2012):

	Year Ended December 31,	
	2014	2013
Risk-free interest rate	1.90%	1.12%
Expected term (in years)	6.25	6.25
Expected volatility	90%	85%
Expected dividend yield	0%	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. In developing a forfeiture rate estimate for pre-vesting forfeitures, we have considered our historical experience of actual forfeitures. If our future actual forfeiture rate is materially different from our estimate, our stock-based compensation expense could be significantly different from what we have recorded in the current period.

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,		
	2014	2013	2012
	(in thousands)		
Research and development	$ 490	$176	$ 68
General and administrative	1,063	219	53
	$1,553	$395	$121

Results of Operations

Comparison of Years Ended December 31, 2014 and 2013

The following table summarizes our results of operations for the years ended December 31, 2014 and 2013:

	Year Ended December 31, 2014	2013	Increase (Decrease)
		(in thousands)	
Statement of Operations Data:			
Revenue	$ —	$ —	$ —
Operating expenses:			
Research and development	27,391	9,561	17,830
General and administrative	8,141	4,219	3,922
Total operating expenses	35,532	13,780	21,752
Loss from operations	(35,532)	(13,780)	(21,752)
Other income (expense):			
Interest income	28	—	28
Interest expense	(870)	—	(870)
Foreign currency transaction gains (losses), net	(104)	(247)	143
Total other income (expense), net	(946)	(247)	(699)
Net loss	$ (36,478)	$ (14,027)	$(22,451)

Research and development expenses

	Year Ended December 31, 2014	2013	Increase (Decrease)
		(in thousands)	
Direct research and development expenses by program:			
Beloranib:			
Pre-clinical and manufacturing	$ 8,077	$ 2,898	$ 5,179
Clinical trials	4,642	2,983	1,659
Licensing, milestone and licensing maintenance fees	7,019	—	7,019
Subtotal	19,738	5,881	13,857
ZGN-839 and other early stage development activities	1,562	295	1,267
Subtotal	21,300	6,176	15,124
Unallocated expenses:			
Personnel related	3,261	1,258	2,003
Consultants	2,359	1,981	378
Other	471	146	325
Subtotal	6,091	3,385	2,706
Total research and development expenses	$ 27,391	$ 9,561	$ 17,830

Research and development expenses for the year ended December 31, 2014 increased $17.8 million compared to the year ended December 31, 2013. The increase was primarily due to increased costs of $13.9 million associated with our beloranib program, $1.3 million associated with ZGN-839 and other early-stage development programs (consisting of our second-generation MetAP2 inhibitors), and $2.7 million in our unallocated expenses. Of the increase in our beloranib program, pre-clinical and manufacturing costs increased by $5.2 million period over

period as a result of our focus on drug manufacturing and other pre-clinical activities related to beloranib in order to prepare for clinical trials, as well as toxicology studies required for our NDA submission. Additionally, clinical trial expenses for beloranib increased by $1.7 million period over period as a result of timing of our clinical trials in 2014 and 2013. Clinical trial activities undertaken by our Australian subsidiary are recorded net of a 45% research and development tax incentive from the Australian government. Lastly, licensing, milestone and licensing maintenance fees increased $7.0 million due to the achievement of a milestone related to the initiation of a first Phase 3 clinical trial in beloranib, which we initiated in September 2014. Costs related to ZGN-839 and other early-stage development programs increased in 2014 as a result of our increased focus on our early-stage programs in 2014. Unallocated expenses increased period over period primarily due to an increase in personnel related costs of $2.0 million and an increase in consultant expenses of $0.4 million. Personnel costs increased due to 11 new employees in 2014, which resulted in a $1.3 million increase in salaries, a $0.4 million increase in bonus, and a $0.3 million increase in stock compensation. Consultant expenses increased due to additional activity with regard to FDA meetings, initiation of clinical trials, and nonclinical activity.

General and administrative expenses

	Year Ended December 31,		Increase (Decrease)
	2014	2013	
		(in thousands)	
Personnel related	$ 3,304	$ 1,358	$ 1,946
Professional fees	3,314	2,463	851
Travel and other	1,523	398	1,125
Total general and administrative expenses	$ 8,141	$ 4,219	$ 3,922

General and administrative expenses for the year ended December 31, 2014 increased $3.9 million compared to the year ended December 31, 2013. The increase was primarily due to increased personnel related costs of $1.9 million, increased travel and other related costs of $1.1 million and increased professional fees of $0.9 million period over period. Of the increase in personnel related expenses the hiring of new employees increased $0.8 million, stock-based compensation increased $0.8 million related to the new employees and bonuses increased $0.3 million. The increase in travel and other related costs is the result of an increase in directors and officer's insurance of $0.5 million due to becoming a public company, an increase of $0.4 million relating to commercial marketing projects as well as various other increases including information technology-related expenses to support our operating as a public company and increased office rent due to the office move in July 2014. The professional fees increase is primarily due to $0.5 million of consulting fees, $0.2 million of attorney fees, and $0.2 million increase in fees for being a public company.

Other income (expense), net

Interest expense. Interest expense for the year ended December 31, 2014 was related to interest expense on our outstanding borrowings under the credit facility that we entered into on March 31, 2014, consisting of $0.9 million of the stated interest of 8.1% per year due on outstanding borrowings, a final payment of 6% of amounts drawn down that is being recorded as interest expense over the term through the maturity date using the effective-interest method, the amortization of deferred financing costs, and the accretion of debt discount relating to the credit facility, both approximately $0.1 million, and $0.2 million related to a fee which was due to the lender upon the completion of our IPO. We had no debt outstanding during 2013.

Foreign currency transaction gains (losses), net. Net foreign currency transaction losses of $0.1 million for the year ended December 31, 2014 were primarily due to the re-measurement of receivables, denominated in Australian dollars, from the Australian government for research and development tax incentives.

Comparison of Years Ended December 31, 2013 and 2012

The following table summarizes our results of operations for the years ended December 31, 2013 and 2012:

	Year Ended December 31, 2013	2012	Increase (Decrease)
		(in thousands)	
Revenue	$ —	$ —	$ —
Operating expenses:			
Research and development	9,561	11,544	(1,983)
General and administrative	4,219	2,247	1,972
Total operating expenses	13,780	13,791	(11)
Loss from operations	(13,780)	(13,791)	11
Other income (expense):			
Interest income	—	—	—
Interest expense	—	(97)	97
Foreign currency transaction gains (losses), net	(247)	8	(255)
Total other income (expense), net	(247)	(89)	(158)
Net loss	$ (14,027)	$ (13,880)	$ (147)

Research and development expenses

	Year Ended December 31, 2013	2012	Increase (Decrease)
		(in thousands)	
Direct research and development expenses by program:			
Beloranib:			
Pre-clinical and manufacturing	$2,898	$ 4,365	$ (1,467)
Clinical trials	2,983	2,437	546
Licensing, milestone and license maintenance fees	—	150	(150)
Subtotal	5,881	6,952	(1,071)
ZGN-839 and other early-stage development	295	2,193	(1,898)
Subtotal	6,176	9,145	(2,969)
Unallocated expenses:			
Personnel related	1,258	902	356
Consultants	1,981	1,371	610
Other	146	126	20
Subtotal	3,385	2,399	986
Total research and development expenses	$9,561	$11,544	$ (1,983)

Research and development expenses for the year ended December 31, 2013 were $9.6 million, compared to $11.5 million for the year ended December 31, 2012. The decrease of $1.9 million was primarily due to the decreased costs of $1.9 million associated with ZGN-839 and other early-stage development programs (consisting of our second-generation MetAP2 inhibitors) and decreased costs of $1.1 million associated with beloranib, partially offset by an increase in consultant expenses of $0.6 million and an increase in personnel related costs of $0.4 million. During 2013, we focused our research and development efforts primarily on our ongoing clinical trials for beloranib as opposed to our early-stage programs. Expenses related to beloranib decreased year over year as a result of a $1.5 million decrease in pre-clinical and manufacturing expenses,

partially offset by an increase of $0.5 million from our clinical trial expenses. Pre-clinical and manufacturing costs decreased year over year as a result of completing a significant portion of our development-enabling toxicology and other pre-clinical activities related to beloranib in 2012. Clinical trial expenses for beloranib increased by $0.5 million year over year as a result of expenses incurred for our 12-week Phase 2a clinical trial for severe obesity and for our 12-week Phase 2a clinical trial for PWS that were both ongoing in 2013, as compared to expenses incurred for our 12-week Phase 2a clinical trial for severe obesity that started in 2012 and for our 4-week Phase 1b clinical trial for severe obesity that was started and completed in 2012. Expenses for our Phase 2a clinical trial for severe obesity, which ran from the third quarter of 2012 through the second quarter of 2013, were recorded net of a 45% research and development tax incentive from the Australian government of $1.2 million and $0.6 million during the years ended December 31, 2013 and 2012, respectively. Consultant costs increased by $0.6 million year over year primarily due to expenses incurred in conjunction with our IND filing for our Phase 2a clinical trial for PWS. Personnel related costs increased by $0.4 million year over year primarily due to the hiring of a new employee of $0.2 million and increased stock-based compensation of $0.1 million.

General and administrative expenses

	Year Ended December 31,		Increase (Decrease)
	2013	2012	
		(in thousands)	
Personnel related	$1,358	$ 910	$ 448
Professional fees	2,463	947	1,516
Travel and other	398	390	8
Total general and administrative expenses	$4,219	$2,247	$ 1,972

General and administrative expenses for the year ended December 31, 2013 were $4.2 million, compared to $2.2 million for the year ended December 31, 2012. The increase of $2.0 million in general and administrative expenses was primarily due to increased professional fees of $1.5 million and increased personnel related costs of $0.4 million year over year. The increase in professional fees consisted primarily of a $1.0 million increase in accounting and audit, legal and investor relations fees due to ongoing business activities as well as an increase of $0.4 million related to two external market research studies that were conducted in 2013. Personnel related costs increased by $0.4 million year over year primarily due to employee salary and bonus increases of $0.2 million and increases in stock-based compensation of $0.2 million.

Other income (expense), net

Interest expense . Interest expense for the year ended December 31, 2012 was related to interest on convertible promissory notes issued in August 2012 that were subsequently converted into shares of our Series D redeemable convertible preferred stock in November 2012. We had no debt outstanding during 2013.

Foreign currency transaction gains (losses), net. Net foreign currency transaction losses of $0.2 million for the year ended December 31, 2013 were primarily due to the re-measurement of receivables, denominated in Australian dollars, from the Australian government for research and development tax incentives, reflecting both a strengthening of the U.S. dollar relative to the Australian dollar and an increase in our receivable balances for such tax incentives during the year ended December 31, 2013.

Liquidity and Capital Resources

As of December 31, 2014, we had cash and cash equivalents and marketable securities totaling $115.5 million. We invest our cash in money market funds, U.S. government securities, corporate bonds, and commercial paper, 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, 2014, we had an accumulated deficit of $105.4 million. We have funded our operations since inception primarily through sales of redeemable convertible preferred stock and, to a lesser extent, through the issuances of convertible promissory notes. In June 2014, we completed an IPO of common stock with net proceeds of $102.7 million, after deducting underwriting discounts and commissions. We also incurred offering costs of $2.5 million related to the IPO.

On January 28, 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 $129.5 million based upon the price of $35.00 per share and after deducting underwriting discounts and commissions, and estimated offering expenses.

On March 31, 2014, we entered into a loan and security agreement, or the 2014 Credit Facility, which provided for initial borrowings of $7.5 million and additional borrowings of up to $12.5 million. On that same date, we received proceeds of $7.5 million from the issuance of promissory notes under a term loan as part of the 2014 Credit Facility. Of the additional $12.5 million of borrowings that was available to us, $7.5 million was available to be drawn down until September 30, 2014 and $5.0 million was available to be drawn down for a 30-day period upon the completion of our IPO that occurred in June 2014. We elected not to draw down the $7.5 million or the $5.0 million and these amounts are no longer available to us. All promissory notes issued under the 2014 Credit Facility are collateralized by substantially all of our personal property, other than our intellectual property. There are no financial covenants associated with the debt facility; however, 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; and certain other business transactions.

Upon entering into this 2014 Credit Facility, we were obligated to make monthly, interest-only payments on any term loans funded under the 2014 Credit Facility until December 1, 2014 and, thereafter, to pay 36 consecutive, equal monthly installments of principal and interest from January 1, 2015 through December 1, 2017. As per the terms of the agreement, in June 2014, upon the completion of our IPO, the term of monthly, interest-only payments was extended until June 1, 2015. Outstanding term loans under the 2014 Credit Facility bear interest at an annual rate of 8.1%. In addition, a final payment equal to 6.0% of any amounts drawn under the facility is due upon the earlier of the maturity date, acceleration of the term loans or prepayment of all or part of the term loans. We were also obligated to pay a separate fee upon any initial public offering; a sale of substantially all of our assets; or a merger, reorganization or sale of our voting equity securities where existing voting stockholders hold less than 50% of voting equity securities after such transaction. During the year ended December 31, 2014, we recorded interest expense of $0.2 million relating to the fee paid to the lender upon completion of our IPO.

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

	Years Ended December 31,		
	2014	2013	2012
		(in thousands)	
Cash used in operating activities	$ (28,241)	$(15,004)	$(13,589)
Cash used in investing activities	(57,315)	(17)	(2)
Cash provided by financing activities	108,142	40,603	22,059
Net increase in cash and cash equivalents	$ 22,586	$ 25,582	$ 8,468

Net cash used in operating activities

During the year ended December 31, 2014, operating activities used $28.2 million of cash, resulting from our net loss of $36.5 million, partially offset by non-cash charges of $5.3 million, and net cash provided by changes in our operating assets and liabilities of $3.2 million. Our net loss was primarily attributed to research and development activities related to our beloranib program, licensing milestones 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, 2014, consisted primarily of common stock issued in lieu of a milestone payment of $3.6 million and stock-based compensation expense of $1.6 million. Net cash provided by changes in our operating assets and liabilities during the year ended December 31, 2014, consisted primarily of a $1.1 million decrease in tax incentive receivable, $0.8 million increase in accounts payable and a $2.3 million increase in accrued expenses, partially offset by a $1.1 million increase in prepaid expenses and other current assets.

During the year ended December 31, 2013, operating activities used $15.0 million of cash, primarily resulting from our net loss of $14.0 million and from net cash used by changes in our operating assets and liabilities of $1.6 million, partially offset by non-cash charges of $0.7 million. Our net loss was primarily attributed to research and development activities related to beloranib and our general and administrative expenses, as we had no revenue in the period. Net cash used by changes in our operating assets and liabilities during the year ended December 31, 2013, consisted primarily of a $1.2 million increase in our research and development tax incentive receivable from the Australian government and a $0.8 million decrease in accrued expenses, partially offset by a $0.2 million decrease in prepaid expenses and other current assets and a $0.2 million increase in accounts payable. Our net non-cash charges during the year ended December 31, 2013, consisted primarily of stock-based compensation expense of $0.4 million and unrealized foreign currency transaction losses of $0.3 million.

During the year ended December 31, 2012, operating activities used $13.6 million of cash, primarily resulting from our net loss of $13.9 million, partially offset by non-cash charges of $0.2 million and by cash provided from changes in our operating assets and liabilities of $0.1 million. Our net loss was primarily attributed to research and development activities related to our beloranib and ZGN-839 programs 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, 2012, primarily consisted of stock-based compensation expense of $0.1 million and non-cash interest expense of $0.1 million. Net cash provided by changes in our operating assets and liabilities during the year ended December 31, 2012, consisted primarily of a $1.0 million increase in accounts payable and accrued expenses, partially offset by a $0.6 million increase in our research and development tax incentive receivable from the Australian government and a $0.3 million increase in prepaid expenses and other current assets. Our prepaid expenses and other current assets, accounts payable and accrued expense balances were affected by the timing of vendor invoicing and payments.

Net cash used in investing activities

During the year ended December 31, 2014, we purchased marketable securities of $57.2 million. We also purchased equipment of $0.1 million and paid a security deposit on our new office lease of $0.1 million. We used an immaterial amount of cash during the years ended December 31, 2013 and 2012 to purchase property and equipment.

Net cash provided by financing activities

During the year ended December 31, 2014, net cash provided by financing activities was $108.1 million as a result of proceeds of $102.7 million from our IPO, net of underwriting discounts and commissions, of $7.4 million from the issuance of debt and of $0.4 million from issuances of our Series E redeemable convertible preferred stock, the total of which was partially offset by payments of $2.3 million of offering costs related to our IPO that were paid during the year.

During the year ended December 31, 2013, net cash provided by financing activities was $40.6 million as a result of net proceeds of $6.0 million from issuances of our Series D redeemable convertible preferred stock and $34.8 million from issuances of our Series E redeemable convertible preferred stock, partially offset by payments of $0.2 million of offering costs made prior to our IPO that we completed in June 2014.

During the year ended December 31, 2012, net cash provided by financing activities was $22.1 million. Net cash provided by financing activities primarily resulted from net proceeds of $16.1 million raised from issuances of our Series C redeemable convertible preferred stock and Series D redeemable convertible preferred stock and net proceeds of $6.0 million from the issuance of convertible promissory notes.

Beloranib is still in clinical development and ZGN-839 and our second-generation MetAP2 inhibitors are in pre-clinical development. We expect to continue to incur significant expenses and increasing operating losses for the foreseeable future. We anticipate that our expenses will increase substantially if and as we:

- advance the clinical development of beloranib as a treatment for obesity and hyperphagia in patients with PWS through Phase 3 clinical trials;
- advance the clinical development of beloranib as a treatment for patients with HIAO;
- initiate IND-enabling studies and clinical development of ZGN-839 and our second-generation MetAP2 inhibitors through the initiation of Phase 1 clinical development;
- advance the clinical development of beloranib as a treatment for severe obesity in the general population through a Phase 2b clinical trial;
- seek to identify additional indications for beloranib;
- 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, 2014, together with the net proceeds of our follow-on offering, that was completed in January 2015, of $129.5 million will enable us to fund our operating expenses and capital expenditure requirements for at least the next 18 months. 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 of beloranib, ZGN-839 and our second-generation MetAP2 inhibitors and because the extent to which we may enter into collaborations with third parties for 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 beloranib, ZGN-839 and our second-generation MetAP2 inhibitors 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 and 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 your rights as a common stockholder. 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 your 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 of beloranib, ZGN-839 or our second-generation MetAP2 inhibitors 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 beloranib, ZGN-839 or our second-generation MetAP2 inhibitors 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 research and development tax credits, due to our uncertainty of realizing a benefit from those items. As of December 31, 2014, we had federal and state net operating loss carryforwards of $17.0 million and $9.6 million, respectively. Our federal net operating loss carryforwards begin to expire in 2026 and our state net operating loss carryforwards begin to expire in 2030. As of December 31, 2014, we also had federal and state research and development tax credit carryforwards of $7.7 million and $1.9 million, respectively, which begin to expire in 2026 and 2021, 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 at December 31, 2014 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)	$ 603	$ 229	$ 374	$ —	$ —
Debt commitments (4)	9,063	1,965	7,098		
Total (2)(3)	$ 9,666	$ 2,194	$7,472	$ —	$ —

(1) We entered into an operating lease for new 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.

(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. For the year ended December 31, 2014, we recorded an expense of $7.0 million in our consolidated financial statements, including $3.3 million that was paid in the form of our common stock (valued at $3.6 million), for milestones achieved under these licensing agreements during 2014. 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, 2014, 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, pre-clinical 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 a 6% final payment of the amounts drawn under the credit facility.

Off-Balance Sheet Arrangements

We did not have during the periods presented, 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

In August 2014, the FASB issued ASU No. 2014-15, *Presentation of Financial Statements—Going Concern* . The new guidance addresses management's responsibility to evaluate whether there is substantial doubt about an entity's ability to continue as a going concern and to provide related footnote disclosures. Management's evaluation should be based on relevant conditions and events that are known and reasonably knowable at the date that the financial statements are issued. The standard will be effective for the first interim period within annual reporting periods beginning after December 15, 2016. Early adoption is permitted. We are evaluating the effect that this guidance will have on our consolidated financial statements.

Item 7A. Quantitative and Qualitative Disclosure about Market Risk

Interest Rate Fluctuation Risk

Our cash, cash equivalents, and marketable securities as of December 31, 2014 consisted of cash, government securities, corporate bonds, commercial paper, 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. However, because of the short-term nature of the instruments in our portfolio, a sudden change in market interest rates would not be expected to have a material impact on our financial condition and/or results of operation.

Foreign Currency Exchange Risk

Foreign currency transaction exposure results primarily from transactions with our 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 of $0.1 million, $0.2 million, and $8,000 were recorded for the years ended December 31, 2014, 2013, and 2012, 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, 2014, a 10% unfavorable movement in foreign currency exchange rates would expose us an increase in net loss. For the year ended December 31, 2014, we estimated that a 10% unfavorable movement in foreign currency exchange rates would have increased our net loss by $0.1 million. This amount is based on a sensitivity analysis performed on our financial position as of December 31, 2014. We have experienced and we will continue to experience fluctuations in our net income (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 SUPPLEMENTARY DATA

INDEX TO CONSOLIDATED FINANCIAL STATEMENTS

Report of Independent Registered Public Accounting Firm

To the Board of Directors and Stockholders of
Zafgen, Inc.:

In our opinion, the accompanying consolidated balance sheets and the related consolidated statements of operations and comprehensive loss, of changes in redeemable convertible preferred stock and stockholders' equity (deficit) and of cash flows present fairly, in all material respects, the financial position of Zafgen, Inc. and its subsidiaries at December 31, 2014 and 2013, and the results of their operations and their cash flows for each of the three years in the period ended December 31, 2014 in conformity with accounting principles generally accepted in the United States of America. These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on these financial statements based on our audits. We conducted our audits of these statements in accordance with the standards of the Public Company Accounting Oversight Board (United States). Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement. An audit includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements, assessing the accounting principles used and significant estimates made by management, and evaluating the overall financial statement presentation. We believe that our audits provide a reasonable basis for our opinion.

/s/ PricewaterhouseCoopers LLP

Boston, Massachusetts
March 24, 2015

ZAFGEN, INC.

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

	December 31, 2014	December 31, 2013
Assets		
Current assets:		
Cash and cash equivalents	$ 58,103	$ 35,517
Marketable securities	57,359	—
Tax incentive receivable	391	1,617
Prepaid expenses and other current assets	1,345	224
Total current assets	117,198	37,358
Property and equipment, net	79	37
Other assets	242	743
Total assets	$ 117,519	$ 38,138
Liabilities, Redeemable Convertible Preferred Stock and Stockholders' Equity (Deficit)		
Current liabilities:		
Accounts payable	$ 2,348	$ 2,015
Accrued expenses	3,172	900
Notes payable, current	1,381	—
Total current liabilities	6,901	2,915
Notes payable, net of discount, long-term	6,177	—
Total liabilities	13,078	2,915
Commitments and contingencies (Note 11)		
Redeemable convertible preferred stock (Series A, B, C, D and E), $0.001 par value;		
No shares and 99,292,610 shares authorized at December 31, 2014 and 2013, respectively; no shares and 94,483,404 shares issued and outstanding at December 31, 2014 and 2013, respectively; aggregate liquidation preference of $104,588 at December 31, 2013	—	103,797
Stockholders' equity (deficit):		
Preferred stock; $0.001 par value; 5,000,000 and no shares authorized at December 31, 2014 and 2013, respectively; no shares issued and outstanding at December 31, 2014 and 2013	—	—
Common stock, $0.001 par value; 115,000,000 shares authorized at December 31, 2014 and 2013; 22,879,160 and 729,391 shares issued and outstanding at December 31, 2014 and 2013, respectively	23	1
Additional paid-in capital	209,838	332
Accumulated deficit	(105,385)	(68,907)
Accumulated other comprehensive loss	(35)	—
Total stockholders' equity (deficit)	104,441	(68,574)
Total liabilities, redeemable convertible preferred stock and stockholders' equity (deficit)	$ 117,519	$ 38,138

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,		
	2014	2013	2012
Revenue	$ —	$ —	$ —
Operating expenses:			
Research and development	27,391	9,561	11,544
General and administrative	8,141	4,219	2,247
Total operating expenses	35,532	13,780	13,791
Loss from operations	(35,532)	(13,780)	(13,791)
Other income (expense):			
Interest income	28	—	—
Interest expense	(870)	—	(97)
Foreign currency transaction gains (losses), net	(104)	(247)	8
Total other income (expense), net	(946)	(247)	(89)
Net loss	(36,478)	(14,027)	(13,880)
Accretion of redeemable convertible preferred stock to redemption value	(92)	(213)	(67)
Net loss attributable to common stockholders	$ (36,570)	$ (14,240)	$ (13,947)
Net loss per share attributable to common stockholders, basic and diluted	$ (3.00)	$ (19.53)	$ (19.65)
Weighted average common shares outstanding, basic and diluted	12,189,155	729,001	709,678
Comprehensive loss:			
Net loss	$ (36,478)	$ (14,027)	$ (13,880)
Other comprehensive loss:			
Unrealized loss on marketable securities	(35)	—	—
Total other comprehensive loss	(35)	—	—
Total comprehensive loss	$ (36,513)	$ (14,027)	$ (13,880)

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

ZAFGEN, INC.

CONSOLIDATED STATEMENTS OF CHANGES IN REDEEMABLE CONVERTIBLE PREFERRED STOCK AND STOCKHOLDERS' EQUITY (DEFICIT)
(In thousands, except share data)

	Series A, B, C, D and E Redeemable Convertible Preferred Stock		Common Stock		Additional	Accumulated	Accumulated Other Comprehensive	Total Stockholders'
	Shares	Amount	Shares	Par Value	Paid-in Capital	Deficit	Loss	Equity (Deficit)
Balances at January 1, 2012	54,553,369	$ 40,575	719,957	$ 1	$ 83	$ (41,000)	$ —	$ (40,916)
Issuance of Series C redeemable convertible preferred stock, net of issuance costs of $8	7,808,400	7,067	—	—	—	—	—	—
Issuance of Series D redeemable convertible preferred stock, net of issuance costs of $54	6,653,988	8,990	—	—	—	—	—	—
Conversion of promissory notes and accrued interest to Series D redeemable convertible preferred stock	4,975,260	6,086	—	—	—	—	—	—
Issuance of common stock upon exercise of stock options	—	—	16,069	—	13	—	—	13
Stock-based compensation expense	—	—	—	—	121	—	—	121
Accretion of redeemable convertible preferred stock to redemption value	—	67	—	—	(67)	—	—	(67)
Net loss	—	—	—	—	—	(13,880)	—	(13,880)
Balances at December 31, 2012	73,991,017	62,785	736,026	1	150	(54,880)	—	(54,729)
Issuance of Series D redeemable convertible preferred stock, net of issuance costs of $1	4,381,914	5,955	—	—	—	—	—	—
Issuance of Series E redeemable convertible preferred stock, net of issuance costs of $156	16,110,473	34,844						
Repurchase and retirement of common stock, at cost	—	—	(6,635)	—	—	—	—	—
Stock-based compensation expense	—	—	—	—	395	—	—	395
Accretion of redeemable convertible preferred stock to redemption value	—	213	—	—	(213)	—	—	(213)
Net loss	—	—	—	—	—	(14,027)	—	(14,027)
Balances at December 31, 2013	94,483,404	103,797	729,391	1	332	(68,907)	—	(68,574)
Issuance of Series E redeemable convertible preferred stock, net of issuance costs of $1	204,101	442	—	—	—	—	—	—
Accretion of redeemable convertible preferred stock to redemption value	—	92	—	—	(92)	—	—	(92)
Conversion of redeemable convertible preferred stock to common stock	(94,687,505)	(104,331)	15,077,621	15	104,316	—	—	104,331
Issuance of common stock	—	—	6,900,000	7	100,157	—	—	100,164
Issuance of common stock upon exercise of stock options	—	—	398	—	3	—	—	3
Issuance of common stock in lieu of milestone payment	—	—	171,750	—	3,569	—	—	3,569
Stock-based compensation expense	—	—	—	—	1,553	—	—	1,553
Unrealized loss on marketable securities	—	—	—	—	—	—	(35)	(35)
Net loss	—	—	—	—	—	(36,478)	—	(36,478)
Balances at December 31, 2014	—	$ —	22,879,160	$ 23	$ 209,838	$ (105,385)	$ (35)	$ 104,441

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

ZAFGEN, INC.

CONSOLIDATED STATEMENTS OF CASH FLOWS
(In thousands)

	Years Ended December 31,		
	2014	2013	2012
Cash flows from operating activities:			
Net loss	$ (36,478)	$(14,027)	$(13,880)
Adjustments to reconcile net loss to net cash used in operating activities			
Stock-based compensation expense	1,553	395	121
Non-cash interest expense	46	—	97
Depreciation expense	16	12	11
Common stock issued in lieu of milestone payment	3,569	—	—
Unrealized foreign currency transaction losses	93	250	—
Premium on marketable securities	(225)	—	—
Amortization of discount on marketable securities	31	—	—
Changes in operating assets and liabilities:			
Prepaid expenses and other current assets	(1,121)	165	(269)
Tax incentive receivable	1,133	(1,237)	(630)
Accounts payable	815	237	727
Accrued expenses	2,327	(799)	234
Net cash used in operating activities	(28,241)	(15,004)	(13,589)
Cash flows from investing activities:			
Purchase of marketable securities	(57,200)	—	—
Purchases of property and equipment	(58)	(17)	(2)
Deposits	(57)	—	
Net cash used in investing activities	(57,315)	(17)	(2)
Cash flows from financing activities:			
Proceeds from issuance of redeemable convertible preferred stock	442	40,799	16,057
Proceeds from issuance of notes payable, net of issuance costs	7,386	—	—
Payments of debt offering costs	(49)	—	—
Issuance of convertible promissory notes, net of issuance costs	—	—	5,989
Proceeds from exercise of common stock options	3	—	13
Proceeds from initial public offering, net of commissions and underwriting discounts	102,672	—	—
Payments of initial public offering costs	(2,312)	(196)	—
Net cash provided by financing activities	108,142	40,603	22,059
Net increase in cash and cash equivalents	22,586	25,582	8,468
Cash and cash equivalents at beginning of period	35,517	9,935	1,467
Cash and cash equivalents at end of period	$ 58,103	$ 35,517	$ 9,935
Supplemental disclosure of non-cash investing and financing activities:			
Accretion of redeemable convertible preferred stock to redemption values	$ 92	$ 213	$ 67
Deferred offering costs included in accounts payable and accrued expenses	$ 148	$ 547	$ —
Conversion of redeemable preferred stock to common stock	$104,331	$ —	$ —
Conversion of milestone liabilities to common stock	$ 3,569	$ —	$ —
Conversion of convertible promissory notes and accrued interest for shares of redeemable convertible preferred stock	$ —	$ —	$ 6,086
Supplemental disclosure of cash flow information:			
Cash paid for interest	$ 632	$ —	$ —

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

ZAFGEN, INC.

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS
(Amounts in thousands, except share and per share data)

1. Nature of the Business and Basis of Presentation

Zafgen, Inc. (the "Company") was incorporated on November 22, 2005 under the laws of the State of Delaware. The Company is a biopharmaceutical company dedicated to significantly improving the health and well-being of patients affected by obesity and complex metabolic disorders. Zafgen is focused on developing novel therapeutics that treat the underlying biological mechanisms through the MetAP2 pathway. Beloranib, the Company's lead product candidate, is a novel, first-in-class, twice-weekly subcutaneous injection being developed for the treatment of multiple indications, including severe obesity in two rare diseases, Prader-Willi syndrome and obesity caused by hypothalamic injury, including craniopharyngioma-associated obesity; and severe obesity in the general population. Since its inception, the Company has devoted substantially all of its efforts to research and development, recruiting management, acquiring operating assets and raising capital.

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 pre-clinical 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 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 products 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 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 significant 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").

On June 24, 2014, the Company completed an initial public offering ("IPO") of its common stock, which resulted in the sale of 6,900,000 shares at a price of $16.00 per share. The Company received net proceeds from the IPO of approximately $102,672 based upon the price of $16.00 per share and after deducting underwriting discounts and commissions paid by the Company. The Company also incurred offering costs of $2,508 related to the IPO.

On January 28, 2015, the Company completed a follow-on offering of its common stock, which resulted in the sale of 3,942,200 shares at a price of $35.00 per share. The Company received net proceeds from the follow-on offering of approximately $129,500 based upon the price of $35.00 per share after deducting underwriting discounts and commissions, and estimated offering expenses. See Note 16—Subsequent Events.

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 at 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 common stock prior to the IPO and 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 and cash equivalents and marketable securities. The Company has all cash and cash equivalents and marketable securities balances at two 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 considers its investment portfolio of investments 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 income (loss) in stockholders' equity (deficit). 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 (deficit) 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. As of December 31, 2014, the Company had recorded $148 of deferred offering costs, included in other assets in the accompanying consolidated balance sheet, in contemplation of the Company's follow-on offering of its common stock, which closed in January 2015. As of December 31, 2013, the Company had recorded $743 of deferred offering costs, included in other assets in the accompanying consolidated balance sheet, in contemplation of the Company's IPO of its common stock, which closed in June 2014.

Property and Equipment

Property and equipment are stated at cost less accumulated depreciation. Depreciation expense is recognized using the straight-line method over a five-year estimated useful life for both furniture and fixtures and office equipment. 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 pre-clinical 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 options and other stock-based awards granted to employees and directors at the fair value on the date of the grant using the Black-Scholes option-pricing model. The fair value of the awards is recognized as expense, net of estimated forfeitures, over the requisite service period, which is generally the vesting period of the respective award. The straight-line method of expense recognition is applied to all awards with service-only conditions.

For stock-based awards granted to consultants and nonemployees, 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 the Company's common stock and updated assumption inputs in the Black-Scholes option-pricing model.

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

The Company recognizes compensation expense for only the portion of awards that are expected to vest. In developing a forfeiture rate estimate, the Company has considered its historical experience to estimate pre-vesting forfeitures for service-based awards.

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's singular focus is on advancing novel therapeutics for patients suffering from severe obesity and obesity-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 (deficit) that result from transactions and economic events other than those with stockholders. For the year ended December 31, 2014, the Company's only element of other comprehensive loss was unrealized loss on marketable securities. For the years ended December 31, 2013 and 2012, there was no difference between net loss and comprehensive loss.

Net Income (Loss) Per Share

Upon the closing of the Company's IPO in June 2014, all of the Company's outstanding redeemable convertible preferred shares were converted into shares of common stock. Prior to this conversion, the Company followed the two-class method when computing net income (loss) per share as the Company had issued shares that meet the definition of participating securities. The two-class method determines net income (loss) per share for each class of common and participating securities according to dividends declared or accumulated and participation rights in undistributed earnings. The two-class method requires income available to common shareholders for the period to be allocated between common and participating securities based upon their respective rights to receive dividends as if all income for the period had been distributed. The Company's redeemable convertible preferred shares contractually entitled the holders of such shares to participate in dividends, but did not contractually require the holders of such shares to participate in losses of the Company. Accordingly, the two-class method did not apply for periods in which the Company reported a net loss or a net loss attributable to common shareholders resulting from dividends or accretion related to its redeemable convertible preferred shares.

Basic net income (loss) per share attributable to common shareholders is computed by dividing the net income (loss) attributable to common shareholders by the weighted average number of common shares outstanding for the period. Diluted net income (loss) per share attributable to common shareholders is computed by dividing the diluted net income (loss) attributable to common shareholders 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 shareholders is the same as basic net loss per common share attributable to common shareholders, since dilutive common shares are not assumed to have been issued if their effect is antidilutive.

Recently Issued and Adopted Accounting Pronouncements

In June 2014, the Financial Accounting Standards Board ("FASB") issued Accounting Standards Update ("ASU") No. 2014-10, *Development Stage Entities* . The amendments in this guidance remove all incremental financial reporting requirements for development stage entities. Among other changes, this guidance will no longer require development stage entities to present inception-to-date information about income statement line items, cash flows, and equity transactions. This guidance is effective for public companies in the first annual period beginning after December 15, 2014. Early application is permitted for interim and annual periods for which financial statements have not yet been issued. The Company early adopted this guidance in the three months ended June 30, 2014 and, as a result, no longer discloses inception-to-date information in its consolidated financial statements.

In August 2014, the FASB issued ASU No. 2014-15, *Presentation of Financial Statements—Going Concern* . The new guidance addresses management's responsibility to evaluate whether there is substantial doubt about an entity's ability to continue as a going concern and to provide related footnote disclosures. Management's evaluation should be based on relevant conditions and events that are known and reasonably knowable at the date that the financial statements are issued. The standard will be effective for the first interim period within annual reporting periods beginning after December 15, 2016. Early adoption is 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 at December 31, 2014 and 2013, 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 includes situations where there is little, if any, market activity for the asset or liability.

The following tables summarize the Company's cash equivalents and marketable securities as of December 31, 2014 and 2013:

	December 31, 2014			
	Total	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Cash equivalents:				
Money market funds	$14,742	$14,742	$ —	$ —
U.S. government securities	27,767	—	27,767	—
Total cash equivalents	42,509	14,742	27,767	—
Marketable securities:				
U.S. government securities	34,191	—	34,191	—
Corporate bonds	22,168	—	22,168	—
Commercial paper	1,000	—	1,000	—
Total marketable securities	57,359	—	57,359	—
Total cash equivalents and marketable securities	$99,868	$14,742	$ 85,126	$ —

	December 31, 2013			
	Total	Quoted Prices in Active Markets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Cash equivalents:				
Money market funds	$26,501	$26,501	$ —	$ —
	$26,501	$26,501	$ —	$ —

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 discount rates currently available to the Company.

Marketable Securities

The following table summarizes the Company's marketable securities as of December 31, 2014:

	December 31, 2014			
	Amortized Cost	Gross Unrealized Gains	Gross Unrealized Losses	Fair Value
Assets:				
U.S. government securities (due within 1 year)	$ 34,200	$ —	$ (9)	$ 34,191
Corporate bonds (due within 1 year)	18,716	—	(18)	18,698
Corporate bonds (due after 1 year through 2 years)	3,478	—	(8)	3,470
Commercial paper (due within 1 year)	1,000	—	—	1,000
	$ 57,394	$ —	$ (35)	$ 57,359

The Company did not have marketable securities at December 31, 2013.

4. Property and Equipment, net

Property and equipment, net consisted of the following as of December 31, 2014 and 2013:

	December 31,	
	2014	2013
Office equipment	$ 79	$ 27
Furniture and fixtures	50	44
	129	71
Less: Accumulated depreciation	(50)	(34)
	$ 79	$ 37

Depreciation expense was $16, $12 and $11 for the years ended December 31, 2014, 2013 and 2012, respectively.

5. Accrued Expenses

Accrued expenses consisted of the following as of December 31, 2014 and 2013:

	December 31,	
	2014	2013
Accrued payroll and related expenses	$1,239	$ 49
Accrued research and development expenses	1,180	616
Accrued professional fees	585	196
Accrued other	168	39
	$3,172	$900

6. Notes Payable

On March 31, 2014, the Company entered into a loan and security agreement with Oxford Finance LLC and Midcap Financial (the "Credit Facility"). The Credit Facility provides for initial borrowings of $7,500 under a term loan ("Term Loan A") and additional borrowings of up to $12,500 under other term loans, for a maximum of $20,000. On March 31, 2014, the Company received proceeds of $7,500 from the issuance of promissory notes under the Term Loan A. Of the additional $12,500 amount that was available, $7,500 ("Term Loan B") was

available to be drawn down until September 30, 2014 and $5,000 ("Term Loan C") was available to be drawn down for a 30-day period upon the completion of the Company's IPO that occurred in June 2014. The Company elected not to draw down Term Loan B or Term Loan C and these amounts are no longer available to the Company. All promissory notes issued under the Credit Facility are collateralized by substantially all of the Company's personal property, other than its intellectual property.

Upon entering into this Credit Facility, the Company was obligated to make monthly, interest-only payments on any term loans funded under the Credit Facility until December 1, 2014 and, thereafter, to pay 36 consecutive, equal monthly installments of principal and interest from January 1, 2015 through December 1, 2017. As per the terms of the agreement, in June 2014, upon the completion of the Company's IPO, the term of monthly, interest-only payments were extended until June 1, 2015. Outstanding term loans under the Credit Facility bear interest at an annual rate of 8.1%. In addition, a final payment equal to 6.0% of any amounts drawn under the Credit Facility is due upon the earlier of the maturity date, acceleration of the term loans or prepayment of all or part of the term loans. The Company accrues the final payment amount due relating to Term Loan A of $450, to outstanding debt by charges to interest expense using the effective-interest method from the date of issuance through the maturity date.

Term Loan A was recorded in the balance sheet net of debt discount of $114 that was related to fees assessed by the lender at the time of borrowing. The debt discount is being accreted to the principal amount of the debt. In addition, deferred financing costs of $49 are being amortized to interest expense using the effective-interest method over the same term. For the year ended December 31, 2014, the company recorded additional interest expense of $50 related to the accretion of debt discount and amortization of deferred financing costs. The effective annual interest rate of the outstanding debt under the Credit Facility is approximately 14%.

The Company was obligated to pay a separate fee upon any IPO; a sale of substantially all of the Company's assets; or a merger, reorganization or sale of the Company's voting equity securities where existing voting stockholders hold less than 50% of voting equity securities after such transaction.

There are no financial covenants associated with the debt facility; however, 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; and certain other business transactions.

The Credit Facility 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 Credit Facility, including cash. These events of default include, among other things, failure to pay any amounts due under the Credit Facility, 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 $250.

Notes payable consist of the following:

	December 31, 2014
Notes payable	$ 7,500
Less: current portion	(1,381)
Notes payable, net of current portion	6,119
Debt discount, net of accretion	(79)
Accretion related to final payment	137
Notes payable, net of discount, long term	$ 6,177

Estimated future principal payments due under the Term Loan A are as follows:

Years Ending December 31,	
2015	$1,381
2016	2,936
2017	3,183
Total	$7,500

During the year ended December 31, 2014, the Company recognized $870 of interest expense related to the Credit Facility.

The Company had no debt outstanding as of December 31, 2013.

7. Redeemable Convertible Preferred Stock

As of December 31, 2013, the Company's Certificate of Incorporation, as amended and restated, authorized the Company to issue 99,292,610 shares of $0.001 par value preferred stock.

The Company has previously issued Series A, Series B, Series C, Series D and Series E redeemable convertible preferred stock (collectively, the "Redeemable Preferred Stock"). The Redeemable Preferred Stock was classified outside of stockholders' equity (deficit) because the shares contain redemption features that were not solely within the control of the Company.

In February 2012, the Company issued 7,808,400 shares of Series C redeemable convertible preferred stock at an issuance price equal to $0.9061 per share and received gross proceeds of $7,075. In connection with this financing, the Company paid total issuance costs of $8.

In November 2012, the Company issued 6,653,988 shares of Series D redeemable convertible preferred stock at an issuance price equal to $1.3592 per share and received gross proceeds of $9,044. In connection with this financing, the Company paid total issuance costs of $54. Additionally, in November 2012, $6,000 of convertible promissory notes and $86 of accrued interest were converted into 4,975,260 shares of Series D redeemable convertible preferred stock.

In January 2013, the Company issued 4,381,914 shares of Series D redeemable convertible preferred stock at an issuance price equal to $1.3592 per share and received gross proceeds of $5,956. In connection with this financing, the Company paid total issuance costs of $1.

In November 2013, the Company issued 16,110,473 shares of Series E redeemable convertible preferred stock at an issuance price equal to $2.1725 per share and received gross proceeds of $35,000. In connection with this financing, the Company paid total issuance costs of $156.

In February 2014, the Company issued 204,101 shares of Series E redeemable convertible preferred stock at an issuance price equal to $2.1725 per share and received gross proceeds of $443. In connection with this financing, the Company paid total issuance costs of $1.

Redeemable Preferred Stock consisted of the following as of December 31, 2013:

	Preferred Shares Authorized	Preferred Shares Issued and Outstanding	Liquidation Preference	Carrying Value	Common Stock Issuable Upon Conversion
Series A redeemable convertible preferred stock	5,363,239	5,363,239	$ 2,250	$ 2,229	854,018
Series B redeemable convertible preferred stock	40,266,246	40,266,246	30,402	30,351	6,411,822
Series C redeemable convertible preferred stock	16,732,284	16,732,284	15,161	15,144	2,664,376
Series D redeemable convertible preferred stock	16,011,162	16,011,162	21,775	21,226	2,549,548
Series E redeemable convertible preferred stock	20,919,679	16,110,473	35,000	34,847	2,565,361
	99,292,610	94,483,404	$ 104,588	$103,797	15,045,125

During the year ended December 31, 2014 all preferred shares issued and outstanding were converted to 15,077,621 shares of common stock.

Prior to the Company's IPO, the holders of the Redeemable Preferred Stock had the following rights and preferences:

Voting Rights

The holders of Redeemable Preferred Stock were entitled to vote, together with the holders of common stock, on all matters submitted to stockholders for a vote. Holders of all Redeemable Preferred Stock had the right to vote the number of shares equal to the number of shares of common stock into which such Redeemable Preferred Stock could convert on the record date for determination of stockholders entitled to vote.

Dividends

The Company could not declare, pay or set aside any dividends on shares of any other class or series of capital stock of the Company unless the holders of the Redeemable Preferred Stock then outstanding first received a dividend on each outstanding share of Redeemable Preferred Stock in an amount at least equal to (i) in the case of a dividend on common stock or any class or series that was convertible into common stock, that dividend per share of Redeemable Preferred Stock as would equal the product of (A) the dividend payable on each share of such class or series determined, if applicable, as if all shares of such class or series had been converted into common stock and (B) the number of shares of common stock issuable upon conversion of a share of Redeemable Preferred Stock, or (ii) in the case of a dividend on any class or series that was not convertible into common stock, at a rate per share of Redeemable Preferred Stock determined by (A) dividing the amount of the dividend payable on each share of such class or series of capital stock by the original issuance price of such class or series of capital stock (subject to appropriate adjustment in the event of any stock dividend, stock split, combination of or other similar recapitalization affecting such shares) and (B) multiplying such fraction by an amount equal to the Original Issue Price (as defined below) of each series of Redeemable Preferred Stock. If the Company declared, paid or set aside, on the same date, a dividend on shares of more than one class or series of capital stock of the Company, the dividend payable to the holders of the Redeemable Preferred Stock would have been calculated based upon the dividend on the class or series of capital stock that would have resulted in the highest Redeemable Preferred Stock dividend. The Original Issue Price for Series A, Series B, Series C, Series D and Series E redeemable convertible preferred stock was $0.419463, $0.75503, $0.9061, $1.3592 and $2.1725, respectively, per share, subject to appropriate adjustment in the event of any stock dividend, stock split, combination or other similar recapitalization with respect to the Redeemable Preferred Stock.

Liquidation Preference

In the event of any liquidation, voluntary or involuntary, exclusive out-license of all or substantially all of the intellectual property of the Company, dissolution or winding up of the Company or Deemed Liquidation Event (as defined below), the Series A, Series B, Series C, Series D and Series E redeemable convertible

preferred stockholders were entitled to receive, in preference to all other stockholders, and to the extent available, an amount equal to the Original Issue Price per share, adjusted for any stock dividends, stock splits or reclassifications, plus all dividends declared but unpaid. In the event that proceeds were not sufficient to permit payment in full to these holders, the proceeds would have been ratably distributed among the Series A, Series B, Series C, Series D and Series E holders in proportion to the full preferential amount each such holder was otherwise entitled to receive.

After payments had been made in full to the holders of the Series A, Series B, Series C, Series D and Series E redeemable convertible preferred stock, then, to the extent available, holders of the common stock and holders of the Series A, Series B, Series C, Series D and Series E redeemable convertible preferred stock would have received the remaining amounts available for distribution ratably in proportion to the number of common shares held by them or issuable to them upon conversion of their redeemable convertible preferred stock into common stock. The distributions were subject to an overall distribution limit of the greater of (i) two times the amount the holders of the Redeemable Preferred Stock were entitled to based on their preference payment and (ii) the amount such holder would have received if such holder had converted shares of the Redeemable Preferred Stock into common stock immediately prior to such dissolution, liquidation, exclusive out-license of all or substantially all of the intellectual property, or winding up of the Company or Deemed Liquidation Event.

Unless the holders of at least 70% of the then outstanding shares of the Redeemable Preferred Stock, voting together as a single class on an as-converted basis, elected otherwise, a Deemed Liquidation Event included a sale of the Company, a sale of the capital stock representing a majority of the voting power or a merger or consolidation of the Company into or with another corporation in which the existing Company held less than a majority of the voting power of the surviving or resulting corporation, or the sale, lease, transfer, exclusive license or other disposition, in a single transaction or series of related transactions, by the Company of all or substantially all of the assets of the Company.

Conversion

Each share of Redeemable Preferred Stock was convertible into common stock at the option of the stockholder at any time after the date of issuance. Each share of the preferred stock automatically converted into shares of common stock, at the applicable Series A, Series B, Series C, Series D and Series E redeemable convertible preferred stock conversion ratio then in effect, upon a qualified public offering with net proceeds of not less than $35,000. The conversion ratio of the Series A, Series B, Series C, Series D and Series E redeemable convertible preferred stock, as defined, was determined by dividing the Original Issue Price of each series of preferred stock by the Conversion Price of each series. The Conversion Price of each series was $2.63422764 for Series A, $4.7415884 for Series B, $5.690308 for Series C, $8.535776 for Series D and $13.6433 for Series E. The Conversion Price was subject to adjustment as set forth in the Company's Certificate of Incorporation, as amended and restated, unless at least a majority of the Series A holders, at least 70% of each of Series B or Series C holders, at least 65% of Series D holders and at least a majority of the Series E holders, voting separately as a class with respect to their series, agreed that no such adjustment would be made to their series. As of December 31, 2013, all outstanding shares of Series A, Series B, Series C, Series D and Series E redeemable convertible preferred stock were convertible into common stock on a 6.28-for-1 basis.

Redemption Rights

At the written election of at least 70% of the holders of the Series A, Series B, Series C, Series D and Series E redeemable convertible preferred stock, voting together as a single class on an as-converted basis, the shares of Series A, Series B, Series C, Series D and Series E redeemable convertible preferred stock outstanding were redeemable, at any time on or after November 22, 2017, in three equal annual installments commencing sixty days after receipt of the required vote at the Original Issue Price per share of Series A, Series B, Series C, Series D and Series E redeemable convertible preferred stock plus all declared but unpaid dividends thereon.

The carrying values of the Series A, Series B, Series C, Series D and Series E redeemable convertible preferred stock were being accreted to their redemption values through their respective redemption dates.

8. Stockholders' Equity

On June 5, 2014, the Company effected a 1-for-6.28 reverse stock split of its issued and outstanding shares of common stock and a proportional adjustment to the existing conversion ratios for each series of redeemable convertible preferred stock. Accordingly, all share and per share amounts for all periods presented in these consolidated financial statements and notes thereto have been adjusted retroactively, where applicable, to reflect this reverse stock split and adjustment of the redeemable convertible preferred stock conversion ratios.

On June 24, 2014, the Company completed an IPO of its common stock, which resulted in the sale of 6,900,000 shares at a price of $16.00 per share. The Company received net proceeds from the IPO of $102,672 based upon the price of $16.00 per share and after deducting underwriting discounts and commissions paid by the Company. The Company also incurred offering costs of $2,508 related to the IPO.

Upon closing of the IPO, all outstanding shares of the Company's redeemable convertible preferred stock were converted into 15,077,621 shares of common stock.

As of December 31, 2014, 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, 2014 and 2013, 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.

During the year ended December 31, 2013, the Company reacquired and retired 6,635 shares of restricted common stock, at cost, that were forfeited by a former employee.

9. Stock-Based Awards

Stock Option Plans

The Company's Amended and Restated 2006 Stock Option Plan (the "2006 Plan") provided for the Company to sell or issue common stock or restricted common stock, or to grant incentive stock options or nonqualified stock options for the purchase of common stock, to employees, members of the board of directors and consultants of the Company. The 2006 Plan was administered by the board of directors, or at the discretion of the board of directors, by a committee of the board. The exercise prices, vesting and other restrictions were determined at the discretion of the board of directors, or a committee of the board of directors if so delegated, except that the exercise price per share of stock options could not be less than 100% of the fair market value of the share of common stock on the date of grant and the term of stock option could not be greater than ten years. The total number of shares of common stock that could have been issued under the 2006 Plan was 1,889,150 shares. Upon closing of the Company's IPO, 168,221 shares reserved and not then subject to outstanding options were transferred to the 2014 Stock Option and Incentive Plan, and no further awards will be made under the 2006 Plan.

On June 5, 2014, the Company's stockholders approved the 2014 Stock Option and Incentive Plan (the "2014 Stock Option Plan"), which became effective upon the completion of the IPO of the Company's shares of common stock in June 2014. The 2014 Stock Option Plan provides for the grant of stock options, stock appreciation rights, restricted stock, restricted stock units, unrestricted stock, performance-share awards and cash-based awards. The number of shares initially reserved for issuance under the 2014 Stock Option Plan is 2,168,221 shares of common stock and may be increased by the number of shares under the 2006 Plan that are not needed to fulfill the Company's obligations for awards issued under the 2006 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 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.

The Company generally grants stock-based awards with service conditions only ("service-based" awards).

As required by the 2006 Plan and 2014 Stock Option Plan, the exercise price for stock options granted is not to be less than the fair value of common shares as of the date of grant. Prior to the IPO, the value of common stock was determined by the board of directors by taking into consideration its most recently available valuation of common shares performed by management and the board of directors as well as additional factors which might have changed since the date of the most recent contemporaneous valuation through the date of grant.

During the year ended December 31, 2014, the Company granted stock options for the purchase of 698,642 shares of common stock, of which options for the purchase of 697,050 shares were granted to employees and options for the purchase of 1,592 shares were granted to a consultant.

2014 Employee Stock Purchase Plan

On June 5, 2014, the Company's stockholders approved the 2014 Employee Stock Purchase Plan. A total of 265,000 shares of common stock were reserved for issuance under this plan. The 2014 Employee Stock Purchase Plan became effective upon the completion of the IPO of the Company's shares of common stock. The first offering period commenced on September 1, 2014 and ended on December 31, 2014. 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. As of December 31, 2014, there are 265,000 shares of common stock available for issuance to participating employees under the plan.

Stock Option Valuation

The fair value of each stock option grant is estimated on the date of grant using the Black-Scholes option-pricing model. The Company historically has been a private company and lacks company-specific historical and implied volatility information. Therefore, it estimates its expected stock volatility based on the historical volatility of a publicly traded set of peer companies 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. 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 expected term of stock options granted to nonemployees is equal to the contractual term of the option award. 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 (the Company did not grant any stock options to employees or directors during the year ended December 31, 2012):

	Year Ended December 31,	
	2014	2013
Risk-free interest rate	1.90%	1.12%
Expected term (in years)	6.25	6.25
Expected volatility	90%	85%
Expected dividend yield	0%	0%

The following table summarizes the Company's stock option activity since December 31, 2013:

	Shares Issuable Under Options	Weighted Average Exercise Price	Average Remaining Contractual Term (In years)	Aggregate Intrinsic Value
Outstanding as of December 31, 2013	1,310,330	$ 1.88	7.8	$ 10,185
Granted	698,642	15.56		
Exercised	(398)	6.78		
Forfeited	—			
Outstanding as of December 31, 2014	2,008,574	$ 6.65	7.7	$222,584
Options vested and expected to vest as of December 31, 2014	2,008,574	$ 6.65	7.7	$222,584
Options exercisable as of December 31, 2014	916,818	$ 1.64	6.3	$ 26,767

The aggregate intrinsic value of stock options is calculated as the difference between the exercise price of the stock options and the fair value of the Company's common stock for those stock options that had exercise prices lower than the fair value of the Company's common stock. The aggregate intrinsic value of stock options exercised was $195 and $12 during the years ended December 31, 2014 and 2012, respectively. No stock options were exercised during the year ended December 31, 2013.

The Company received cash proceeds from the exercise of stock options of $3 and $13 during the years ended December 31, 2014 and 2012, respectively.

The weighted average grant-date fair value of stock options granted to employees and directors during the years ended December 31, 2014 and 2013 was $11.73 and $1.83 per share, respectively. The Company did not grant stock options to employees or directors in 2012. The grant of stock options in 2012 was to a consultant.

As of December 31, 2014, there were outstanding unvested service-based stock options held by nonemployees for the purchase of 13,205 shares of common stock. Additionally as of December 31, 2014, there were outstanding unvested performance-based stock options held by nonemployees for the purchase of 796 shares of common stock.

Restricted Common Stock

The 2006 Plan provides for the award of restricted stock. The Company has granted restricted common stock with time-based vesting conditions. Unvested shares of restricted common stock may not be sold or transferred by the holder. These restrictions lapse according to the time-based vesting conditions of each award. The Company values restricted common stock on the grant date using the grant-date market price of the Company's common stock.

The aggregate intrinsic value of restricted stock awards that vested during each of the years ended December 31, 2013 and 2012 was $38 and $22, respectively. The aggregate intrinsic value of restricted stock awards is calculated as the difference between the grant-date fair value of the restricted stock awards and the fair value of the Company's common stock. The Company did not grant any restricted stock awards during the years ended December 31, 2014, 2013 or 2012. As of December 31, 2014 and 2013, there were no unvested restricted stock awards subject to repurchase.

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 statements of operations:

	Year Ended December 31,		
	2014	2013	2012
Research and development	$ 490	$ 176	$ 68
General and administrative	1,063	219	53
	$ 1,553	$ 395	$ 121

As of December 31, 2014, the Company had an aggregate of $8,357 of unrecognized stock-based compensation cost, which is expected to be recognized over a weighted average period of 3.3 years.

10. Net Loss Per Share

Basic and diluted net loss per share attributable to common stockholders was calculated as follows:

	Year Ended December 31,		
	2014	2013	2012
Basic and diluted net loss per share attributable to common stockholders:			
Numerator:			
Net loss	$ (36,478)	$ (14,027)	$ (13,880)
Accretion of redeemable convertible preferred stock to redemption value	(92)	(213)	(67)
Net loss attributable to common stockholders	$ (36,570)	$ (14,240)	$ (13,947)
Denominator:			
Weighted average common shares outstanding, basic and diluted	12,189,155	729,001	709,678
Net loss per share attributable to common stockholders, basic and diluted	$ (3.00)	$ (19.53)	$ (19.65)

The Company excluded the following common stock equivalents, outstanding as of December 31, 2014, 2013 and 2012, from the computation of diluted net loss per share attributable to common stockholders for the years ended December 31, 2014, 2013 and 2012 because they had an anti-dilutive impact due to the net loss attributable to common stockholders incurred for the periods:

	As of December 31,		
	2014	2013	2012
Options to purchase common stock	2,008,574	1,310,330	591,427
Unvested restricted common stock	—	—	10,615
	2,008,574	1,310,330	602,042

11. Commitments and Contingencies

Leases

On May 15, 2014, the Company entered into a new lease for office space in Boston, Massachusetts, effective as of July 28, 2014, with a term expiring July 31, 2017 and an option to extend the lease for three additional years.

Future minimum lease payments for its operating lease as of December 31, 2014 were as follows:

Years Ending December 31,	
2015	$229
2016	235
2017	139
	$603

During the years ended December 31, 2014, 2013 and 2012, the Company recognized $160, $105 and $129, 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. Related to these license agreements, the Company recorded research and development expenses in its consolidated statements of operations as follows:

	Year Ended December 31,		
	2014	2013	2012
License, milestone, and license maintenance fees	$7,019	$—	$150
	$7,019	$—	$150

During the year ended December 31, 2014, the Company recorded expenses of $7,019 relating to milestones achieved in September 2014 upon the initiation of a first Phase 3 clinical trial including the cost of the issuance of common stock valued at $3,569. As of December 31, 2014, the Company is obligated to make additional milestone payments of up to $12,250 upon reaching certain pre-commercialization milestones, such as clinical trials and government approvals, and up to $12,500 upon reaching certain product commercialization milestones. Under one of the license agreements, the Company is also obligated to pay up to $1,250 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. 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, 2014, 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 its board of directors 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, 2014.

12. Income Taxes

During the years ended December 31, 2014, 2013 and 2012, 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:

	2014	2013	2012
Domestic	$(35,818)	$(12,325)	$(13,142)
Foreign	(660)	(1,702)	(738)
Loss before income taxes	$(36,478)	$(14,027)	$(13,880)

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,		
	2014	2013	2012
Federal statutory income tax rate	(34.0%)	(34.0%)	(34.0%)
Federal and state research and development tax credit	(4.4)	(9.0)	(1.2)
State taxes, net of federal benefit	(4.0)	(4.0)	(5.0)
Orphan drug tax credit	(3.2)	(3.1)	—
Stock compensation expense	0.6	0.6	0.2
Nondeductible Australia research and development expenses	0.6	4.1	1.8
Other items	2.4	—	—
Change in deferred tax asset valuation allowance	42.0	45.4	38.2
Effective income tax rate	0.0%	0.0%	0.0%

Net deferred tax assets as of December 31, 2014 and 2013 consisted of the following:

	December 31,	
	2014	2013
Current deferred tax assets:		
Accrued expenses	$ 431	$ 18
Other temporary differences	6	2
Total current deferred tax assets	437	20
Noncurrent deferred tax assets:		
Capitalized research and development expenses	28,609	19,856
Net operating loss carryforwards	6,276	4,021
Tax credit carryforwards	8,934	5,579
Capitalized legal expenses	1,229	790
Stock-based compensation	428	91
Total noncurrent deferred tax assets	45,476	30,337
Total gross deferred tax assets	45,913	30,357
Valuation allowance	(45,913)	(30,357)
Net deferred tax assets	$ —	$ —

Changes in the valuation allowance for deferred tax assets during the years ended December 31, 2014, 2013 and 2012 related primarily to the increase in net operating loss carryforwards, capitalized research and development expenses and research and development tax credit carryforwards and were as follows:

	Year Ended December 31,		
	2014	2013	2012
Valuation allowance as of beginning of year	$30,357	$24,006	$18,744
Decreases recorded as benefit to income tax provision	—	—	—
Increases recorded to income tax provision	15,556	6,351	5,262
Valuation allowance as of end of year	$45,913	$30,357	$24,006

As of December 31, 2014, the Company had net operating loss carryforwards for federal and state income tax purposes of $16,963 and $9,637, respectively, which begin to expire in 2026 and 2030, respectively. The Company also had an additional $16 of federal and state net operating losses not reflected above that were attributable to stock option exercises, which will be recorded as an increase in additional paid-in capital once they are realized in accordance with accounting for stock-based compensation awards. As of December 31, 2014, the Company also had available research and development tax credit carryforwards for federal and state income tax purposes of $7,699 and $1,870, respectively, which begin to expire in 2026 and 2021, respectively. Utilization of the net operating loss carryforwards and research and development 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 shareholders 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 research and development 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 research and development 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, 2014 and 2013, the Company's gross deferred tax asset balance of $45,913 and $30,357, respectively, was comprised principally of net operating loss carryforwards, capitalized research and development expenses and research and development tax credit carryforwards. During the years ended December 31, 2014, 2013 and 2012, gross deferred tax assets increased due to additional net operating loss carryforwards, research and development tax credits generated and additional research and development expenses capitalized for tax purposes.

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, 2014 and 2013. 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, 2014 or 2013.

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 2011 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.

13. Retirement Plan

The Company has a Savings Incentive Match Plan for employees. Under the terms of the plan, the Company contributes 2% of an employee's annual base salary, up to a maximum of the annual Internal Revenue Service compensation limits, for all full-time employees. During the years ended December 31, 2014, 2013 and 2012, the Company recognized $61, $26 and $16, respectively, of expense related to its contributions to the plan.

14. 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 45% refundable tax incentive for qualified research and development activities. For the years ended December 31, 2014, 2013 and 2012, $424, $1,237 and $630, respectively, was recorded as a reduction to research and development expenses in the consolidated statements of operations. These amounts represented 45% 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, 2014 and 2013, the Company recorded in its consolidated statements of operations unrealized foreign currency exchange (gains) losses of $104 and $250, respectively, related to this tax incentive receivable. The Company did not have any foreign exchange gains or losses related to this receivable for the year ended December 31, 2012. As of December 31, 2014 and 2013, the Company's tax incentive receivable from the Australian government was $391 and $1,617, respectively.

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, 2014	June 30, 2014	September 30, 2014	December 31, 2014
Revenue	$ —	$ —	$ —	$ —
Operating expenses	4,521	5,986	14,361	10,664
Net loss attributable to common stockholders	(4,507)	(6,443)	(14,689)	(10,931)
Net loss per share attributable to common stockholders, basic and diluted	$ (6.18)	$ (2.96)	$ (0.65)	$ (0.48)
Weighted average common shares outstanding, basic and diluted	729,391	2,178,465	22,707,012	22,783,817

	Three Months Ended			
	March 31, 2013	June 30, 2013	September 30, 2013	December 31, 2013
Revenue	$ —	$ —	$ —	$ —
Operating expenses	3,520	2,975	3,524	3,761
Net loss attributable to common stockholders	(3,594)	(3,190)	(3,557)	(3,899)
Net loss per share attributable to common stockholders, basic and diluted	$ (4.94)	$ (4.37)	$ (4.88)	$ (5.35)
Weighted average common shares outstanding, basic and diluted	727,763	729,391	729,391	729,391

16. Subsequent Events

In January 2015, the Company completed a follow-on offering resulting in the sale of 3,942,200 common shares at $35.00 per share, including 504,200 shares related to the exercise of the over allotment option by the underwriters. Net proceeds were approximately $129,500 after deducting underwriting discounts and commissions, and estimated offering expenses.

ITEM 9. CHANGES IN AND DISAGREEMENTS WITH ACCOUNTANTS ON ACCOUNTING AND FINANCIAL DISCLOSURE

Changes in Accounting Firm Relationships

We dismissed Edelstein and Company LLP as our independent registered public accounting firm on July 12, 2013, and therefore the firm was not asked to report on our consolidated financial statements for the year ended December 31, 2012. Our board of directors approved our change in accountants. The reports of Edelstein and Company LLP on our consolidated financial statements for the fiscal years ended December 31, 2011 and 2010 contained no adverse opinion or disclaimer of opinion and were not qualified or modified as to audit scope, accounting principle or uncertainty, except that the reports of Edelstein and Company LLP included an emphasis of matter regarding the Company's ability to continue as a going concern. During the fiscal years December 31, 2011 and 2010 and through July 12, 2013 there were no disagreements with Edelstein and Company LLP on any matter of accounting principles or practices, financial statement disclosure, or auditing scope or procedure which if not resolved to the satisfaction of Edelstein and Company LLP would have caused Edelstein and Company LLP to make reference thereto in their reports on our consolidated financial statements for such years.

We subsequently engaged PricewaterhouseCoopers LLP, or PwC, as our independent registered public accounting firm in July 2013. Our audit committee of our board of directors approved this engagement. Prior to Edelstein and Company LLP's dismissal and prior to the appointment of PwC, we did not consult with PwC regarding the application of accounting principles to a specific completed or contemplated transaction or regarding the type of audit opinion that might be rendered on our consolidated financial statements.

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, 2014, 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

This Annual Report on Form 10-K does not include a report of management's assessment regarding internal control over financial reporting or an attestation report of the Company's independent registered public accounting firm due to a transition period established by rules of the Securities and Exchange Commission for newly public companies.

Changes in Internal Control Over Financial Reporting

There were no changes in our internal control over financial reporting (as defined in Rules 13a-15(f) or 15d-15(d) under the Exchange Act) during the period covered by this report 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, 2014.

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, 2014.

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, 2014.

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, 2014.

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, 2014.

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 94 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)

Exhibit No.	Description
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)
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#	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)
10.16	Letter by and between the Registrant and Patrick Loustau, dated June 3, 2014 (incorporated by reference to Exhibit 10.16 of the Registrant's Registration Statement on Form S-1 (File No. 333-195391) filed on June 18, 2014)
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

Exhibit No.	Description
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, 2014 and 2013, (b) our Consolidated Statements of Operations and Comprehensive Loss for the Years Ended December 31, 2014, 2013 and 2012, (c) our Consolidated Statements of Changes in Redeemable Convertible Preferred Stock and Stockholders' Equity (Deficit), (d) our Consolidated Statements of Cash Flows for the Years Ended December 31, 2014, 2013 and 2012 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.

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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 24, 2015

By: /s/ Thomas E. Hughes, Ph.D.
Thomas E. Hughes, Ph.D.
Chief Executive Officer
(*Principal Executive Officer*)

Date: March 24, 2015

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/ Thomas E. Hughes, Ph.D. Thomas E. Hughes, Ph.D.	Chief Executive Officer and Director *(Principal Executive Officer)*	March 24, 2015
/s/ Patricia L. Allen Patricia L. Allen	Chief Financial Officer *(Principal Financial and Accounting Officer)*	March 24, 2015
/s/ Peter Barrett, Ph.D. Peter Barrett, Ph.D.	Chairman of the Board of Directors	March 24, 2015
/s/ Bruce Booth, Ph.D. Bruce Booth, Ph.D.	Director	March 24, 2015
/s/ Avi Goldberg Avi Goldberg	Director	March 24, 2015
/s/ Frances K. Heller Frances K. Heller	Director	March 24, 2015
/s/ John L. LaMattina, Ph.D. John L. LaMattina, Ph.D.	Director	March 24, 2015
/s/ Kevin P. Starr Kevin P. Starr	Director	March 24, 2015
/s/ Frank E. Thomas Frank E. Thomas	Director	March 24, 2015

EXHIBIT 23.1

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We hereby consent to the incorporation by reference in the Registration Statement on Form S-8 (No. 333-196900) of Zafgen, Inc. of our report dated March 24, 2015 relating to the consolidated financial statements, which appears in this Form 10-K.

/s/ PricewaterhouseCoopers LLP

Boston, Massachusetts
March 24, 2015

Exhibit 31.1

CERTIFICATIONS UNDER SECTION 302

I, Thomas E. Hughes, certify that:

1. I have reviewed this annual report on Form 10-K 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)) 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) 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

c) 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 24, 2015

/s/ Thomas E. Hughes
Thomas E. Hughes
Chief Executive Officer
(Principal Executive Officer)

Exhibit 31.2

CERTIFICATIONS UNDER SECTION 302

I, Patricia Allen, certify that:

1. I have reviewed this annual report on Form 10-K 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)) 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) 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

c) 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 24, 2015

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

Exhibit 32.1

CERTIFICATIONS UNDER SECTION 906

Pursuant to section 906 of the Sarbanes-Oxley Act of 2002 (subsections (a) and (b) of section 1350, chapter 63 of title 18, United States Code), each of the undersigned officers of Zafgen, Inc., a Delaware corporation (the "Company"), does hereby certify, to such officer's knowledge, that:

The Annual Report for the year ended December 31, 2012 (the "Form 10-K") of the Company fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934, and the information contained in the Form 10-K fairly presents, in all material respects, the financial condition and results of operations of the Company.

Dated: March 24, 2015

/s/ Thomas E. Hughes
Thomas E. Hughes
Chief Executive Officer
(Principal Executive Officer)

Dated: March 24, 2015

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