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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, 2012

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 001-33415

OREXIGEN THERAPEUTICS, INC.

(Exact name of registrant as specified in its charter)

Delaware	**65-1178822**
(State or Other Jurisdiction of Incorporation or Organization)	*(I.R.S. Employer Identification No.)*
3344 N. Torrey Pines Ct., Suite 200 La Jolla, California	**92037**
(Address of Principal Executive Offices)	*(Zip Code)*

(858) 875-8600

(Registrant's Telephone Number, Including Area Code)

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

Title of Each Class	Name of Exchange on Which Registered
Common Stock, $0.001 par value	**The NASDAQ Global Market**

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

None

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes ☐ No ☑

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or 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 the definitions of "large accelerated filer," "accelerated filer" and "smaller reporting company" in Rule 12b-2 of the Exchange Act. (Check one):

Large accelerated filer ☐	Accelerated filer ☑	Non-accelerated filer ☐ (Do not check if a smaller reporting company)	Smaller reporting company ☐

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

As of June 30, 2012, the aggregate market value of voting stock held by nonaffiliates of the registrant was approximately $318.3 million based on the closing stock price as reported by the NASDAQ Global Market for such date. Shares of common stock held by each officer and director and by each person or group who owns 5% or more of the outstanding common stock have been excluded in that such persons or groups may be deemed to be affiliates. This determination of affiliate status is not necessarily a conclusive determination for other purposes.

As of March 11, 2013, the Registrant had 92,598,625 shares of its $0.001 par value common stock outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant's Definitive Proxy Statement to be filed with the Securities and Exchange Commission pursuant to Regulation 14A in connection with the registrant's 2013 Annual Meeting of Stockholders are incorporated by reference into Part III of this Report. Such proxy statement will be filed with the Securities and Exchange Commission subsequent to the date hereof but not later than 120 days after registrant's fiscal year ended December 31, 2012.

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PART 1

FORWARD-LOOKING STATEMENTS

This Annual Report on Form 10-K and the information incorporated herein by reference contain certain forward-looking statements within the meaning of Section 21E of the Securities Exchange Act of 1934, as amended, and is subject to the Safe Harbor provisions created by that statute . Forward-looking statements are based on our management's beliefs and assumptions and on information currently available to our management. All statements other than statements of historical facts are "forward-looking statements" for purposes of these provisions. Forward-looking statements can be identified by the use of forward-looking words such as "believes," "expects," "hopes," "may," "will," "plans," "intends," "indicates," "suggests," "assuming," "designed," "estimates," "could," "should," "would," "continue," "seeks," "aims," "projects," "predicts," "pro forma," "anticipates," "potential," "probability" or other similar expressions that are intended to identify forward-looking statements. These statements are based on our current beliefs and expectations.

These statements include but are not limited to statements regarding: the Special Protocol Assessment, or SPA, and the protocol for the Contrave ® cardiovascular outcomes trial, or Light Study; the potential for, and timing of, the accrual and adjudication of major adverse cardiovascular events, or MACE; the expected retention rate for patients in the Light Study; the probability of success of the Light Study; the potential for, and timing of, resubmission and approval of a New Drug Application, or NDA, for Contrave based on interim results of the Light Study; the possibility of resubmitting the Contrave NDA with the independent Data Monitoring Committee report on the interim analysis and without the clinical study report for the interim analysis; the potential to accelerate the timing of the review of the Contrave NDA; the safety and effectiveness of Contrave; the potential for past Contrave clinical trials to predict the outcome of future Contrave clinical trials; the potential to demonstrate the real world weight loss potential of Contrave with a commercially available comprehensive lifestyle intervention program; the potential to enter into a collaborative partnership to fund Phase III development and, if approved, commercialization of Empatic™; and the potential for the FDA to approve an NDA for Empatic without requiring data from a cardiovascular outcomes trial in addition to the data obtained from the Light Study. The inclusion of forward-looking statements should not be regarded as a representation by us that any of our plans will be achieved. Actual results may differ materially from those expressed or implied in this report by the forward-looking statements due to the risk and uncertainties inherent in our business, including: the possibility that the FDA determines not to initiate review of the Contrave NDA until it has received the complete study report for the interim analysis; the SPA is not binding on the FDA if public health concerns unrecognized at the time the SPA agreement was entered into become evident, other new scientific concerns regarding product safety or efficacy arise, or if we fail to comply with the agreed upon trial protocol; our ability to conduct the Light Study and the progress and timing thereof, including risks associated with enrolling and retaining the appropriate patients in the Light Study; our ability to demonstrate in the Light Study that the risk of MACE in overweight and obese patients treated with Contrave does not adversely affect Contrave's benefit-risk profile; the potential that earlier clinical trials may not be predictive of future results in the Light Study; the potential for the FDA to not approve Contrave even after the resubmission with the MACE data; the potential for the Light Study to cost more than what is projected; the potential for early termination of our North American collaboration agreement with Takeda Pharmaceutical Company Limited; the costs and time required to complete additional clinical, non-clinical or other requirements prior to any resubmission of the Contrave NDA; the therapeutic and commercial value of Contrave; estimates of the potential market for our product candidates; our ability to maintain sufficient capital to fund our operations through potential approval of Contrave in 2014; the development plan for Empatic; our ability to enter into a collaborative partnership for Empatic on acceptable terms, if at all; the scope of our intellectual property protection for Contrave and Empatic; estimates of the capacity of manufacturing and other facilities to support our product candidates; and the other risks and uncertainties discussed under the heading "Item 1A—Risk Factors," and elsewhere in this in this Annual Report on Form 10-K.

Given these risks and uncertainties, we urge you not to place undue reliance on these forward-looking statements, which speak only as of the date of this report. You should read this Annual Report on Form 10-K

completely and with the understanding that our actual future results may be materially different from what we expect. We hereby qualify our forward-looking statements by these cautionary statements. Except as required by law, we undertake no obligation to update publicly any forward-looking statements or to update the reasons actual results could differ materially from those anticipated in these forward-looking statements, whether as a result of new information, future events, or for any other reason.

Item 1. Business.

Overview

Orexigen® Therapeutics, Inc. ("Orexigen", "we", "our" and "us") is a biopharmaceutical company focused on the development of pharmaceutical product candidates for the treatment of obesity. Our product candidates are Contrave ®, which has completed Phase III clinical trials and which is currently being studied in a cardiovascular outcomes trial, and Empatic™, which has completed Phase II clinical trials. Each of these product candidates is a combination of generic drug components, each of which has already received regulatory approval for other indications and been commercialized. Contrave is a combination of two well-established drugs, bupropion and naltrexone, each in a sustained release, or SR, formulation. Bupropion is a widely prescribed antidepressant and smoking cessation medication; naltrexone is a treatment for alcohol and opioid addiction. Empatic is a combination of bupropion and zonisamide, each in an SR formulation. Zonisamide, in an immediate release formulation, was approved in the United States for the adjunctive treatment of partial seizures, a form of epilepsy. We are developing these combinations in an effort to demonstrate adequate efficacy and safety for potential regulatory approval. We have not yet received regulatory approval for either product candidate.

Both Contrave and Empatic regulate appetite and energy expenditure through central nervous system, or CNS, activity. Results from our clinical trials to date for both Contrave and Empatic have supported our understanding regarding CNS regulation of appetite and energy expenditure. All four of our completed Phase III clinical trials evaluating Contrave met their co-primary endpoints as well as key secondary endpoints, showing a significant reduction in body weight, improvements in cardiovascular and metabolic risk factors and reductions in selected food craving measures. In these four 56-week, randomized, double-blinded, placebo-controlled trials, which together formed our Contrave Obesity Research, or COR, program, Contrave was generally well tolerated by patients, with an overall safety profile that was consistent with its individual components. We believe the results from the COR program of more than 4,500 patients exceed the FDA's categorical efficacy benchmark for clinically significant weight loss. Results from our Phase II and Phase IIb clinical trials evaluating Empatic have also demonstrated what we believe to be robust efficacy and acceptable safety and tolerability. Our latest Phase IIb clinical trial for Empatic was a 24-week, double-blind, randomized, placebo-controlled trial that evaluated 729 patients. This Phase IIb trial met its primary efficacy endpoint by demonstrating statistically significant greater weight loss for both Empatic doses administered in the trial compared to the monotherapies and placebo.

We submitted a New Drug Application, or NDA, for Contrave to the U.S. Food and Drug Administration, or FDA, in March 2010. In December 2010, the FDA's Endocrinologic and Metabolic Drugs Advisory Committee, or the EMDAC, voted 13 to 7 that the available clinical data adequately demonstrate that the potential benefits of Contrave outweigh the potential risks when used long-term in a population of overweight and obese individuals and supported approval. The EMDAC also voted 11 to 8 (with one EMDAC member abstaining from the vote) that a dedicated study to examine the drug's effect on risk for major adverse cardiac events, or MACE, should be conducted as a post-approval requirement versus pre-approval. In January 2011, we received a complete response letter, or CRL, from the FDA regarding our NDA for Contrave. A CRL is issued by the FDA when the review of an NDA is completed and questions remain that preclude the approval of the NDA in its current form. The CRL for Contrave indicated that the FDA could not approve the NDA in its present form primarily due to concerns regarding the cardiovascular safety profile of Contrave when used long-term in a population of overweight and obese patients. The CRL stated that before our NDA could be approved, we must conduct a randomized, double-blind, placebo-controlled trial of sufficient size and duration to demonstrate that the risk of MACE in overweight and obese patients treated with Contrave does not adversely affect the drug's benefit-risk profile.

In September 2011, following a meeting with senior officials in the FDA's Office of New Drugs, or OND, we received written correspondence from the director of the OND detailing the OND's design requirements for a randomized, double-blind, placebo-controlled cardiovascular outcomes trial, or CVOT, for Contrave that would address the CRL. The CVOT is a randomized, double-blind, placebo-controlled cardiovascular outcomes trial evaluating the occurrence of MACE in patients participating in the study. Importantly, the OND stated that if the interim analysis meets the specified criteria to exclude an unacceptable increased cardiovascular risk, Contrave could be approved prior to completion of the CVOT, providing the certainty that we required to conduct the CVOT. If the interim analysis excludes a doubling of risk of MACE in patients receiving Contrave compared to placebo, we plan to resubmit the Contrave NDA to the FDA for approval. The exclusion of a doubling of risk of MACE was established as the threshold for approvability of Contrave during discussions with the FDA prior to the start of the CVOT. An interim analysis and NDA resubmission is planned once the CVOT's independent Data Monitoring Committee has determined that sufficient information has been gathered for the analysis that would include at least 87 adjudicated MACE. In February 2012, we reached agreement with the FDA on a Special Protocol Assessment, or SPA, for the CVOT. An SPA is a written agreement with the FDA on the details of the design and planned analysis for a clinical trial. An SPA is generally binding upon the FDA unless a substantial scientific issue essential to determining safety or efficacy is identified after the trial begins.

In October 2012, we announced that we received a response to a formal dispute resolution request from the FDA's Center for Drug Evaluation and Research, or CDER. We had requested that Contrave be considered for approval on the basis of existing data together with a postmarketing requirement to supply the interim analysis of the CVOT shortly after approval. CDER denied this request, reaffirming that the cardiovascular outcomes data from the interim analysis of the CVOT is required prior to approval; however, CDER indicated that it was highly supportive of the exploration of a faster path to resubmission of the Contrave NDA. In January 2013, the FDA's Division of Metabolism and Endocrinology Products, or DMEP, proposed a resubmission procedure that would allow the independent Data Monitoring Committee's summary report of the CVOT interim analysis to form the basis of the resubmission of the Contrave NDA. The complete clinical study report, or CSR, for the interim analysis, which would ordinarily form the basis for the NDA resubmission filing, would be provided to the FDA during its review of the NDA within 60 days of the NDA resubmission.

We initiated the CVOT, which we refer to as the Light Study, in June 2012, and completed screening in December 2012, which resulted in approximately 8,900 patients randomized to treatment. We enrolled a patient population that we predicted would have an annualized MACE rate between 1% and 2%. The timing of the interim analysis and the Contrave NDA resubmission is dependent on the timing of MACE observed in the Light Study. The observed MACE rate may differ materially from modeled MACE rate. We are preparing to be ready to conduct the interim analysis and resubmit the Contrave NDA in 2013. However, if the observed MACE rate is at or near the low end of the targeted range of 1% to 2%, the resubmission of the Contrave NDA may not occur until early 2014.

In our recent series of discussions with the FDA on the continued development of Empatic, the FDA stated that Phase III data for Empatic may be sufficient to support submission of an NDA without data from a cardiovascular outcomes trial. The FDA indicated that as long as the placebo-subtracted changes in body weight, blood pressure and heart rate for Empatic are similar to or more favorable than the placebo-subtracted changes observed with Contrave, and there are no signals of cardiovascular concern in the Empatic development program, reassuring results of a cardiovascular outcomes trial with Contrave will be sufficient. In addition, while the FDA reiterated its belief that the preclinical teratogenicity data for zonisamide and the pregnancy outcome data with Empatic from the Phase II clinical trials are very concerning, it will allow Phase III studies of Empatic to include women of childbearing potential with a body mass index, or BMI, >27kg/m^2 in the presence of at least one weight-related comorbidity such as hypertension, type 2 diabetes mellitus or dyslipidemia and a BMI >30 kg/m^2 without additional restrictions if appropriate safety measures and adequate informed consent are provided. The FDA noted that similar safety measures and understanding of risk in the Phase III trials may need to be applied in the intended marketed population if Empatic is approved. The FDA added that additional worrisome pregnancy outcome data in the Empatic trials may have an impact on approvability, labeling or a Risk Evaluation and

Mitigation Strategy, or REMS. Prior to initiating Phase III studies of Empatic, we plan to seek a collaboration partner to help fund Phase III clinical development and, if approved, commercialization of Empatic.

We maintain an aggressive intellectual property strategy, which includes patent and trademark filings in multiple jurisdictions including the United States and other commercially significant markets. We hold patents in the United States and Europe that cover the composition of Contrave (bupropion and naltrexone, both in an SR formulation), as well as the use of Contrave for the treatment of obesity. These U.S. patents expire in 2025 and 2024, respectively. We also hold an exclusive license to an issued U.S. patent covering the Empatic composition and methods of use in obesity. This patent expires in 2023. In addition, we own or have exclusive rights to numerous patent applications currently pending in the United States and in jurisdictions outside of the United States with respect to various compositions, methods of use and formulations relating to Contrave and/or Empatic.

We are developing our product candidates for large markets traditionally served by primary care physicians. In order to effectively promote Contrave to these physicians, in September 2010, we entered into a collaboration agreement with Takeda Pharmaceutical Company Limited, or Takeda, to develop and commercialize Contrave in the United States, Canada and Mexico. Subject to certain terms and conditions, the collaboration agreement allows us to co-promote Contrave in the United States. We currently retain marketing rights for Contrave outside the United States, Canada and Mexico and worldwide marketing rights for Empatic. We may consider entering into additional collaborations with other pharmaceutical companies for territories outside the United States, Canada and Mexico and/or for Empatic with the sales force and marketing resources to adequately address the large primary care physician audience. We may also consider utilizing the resources of a contract sales organization or other third-party vendor to optimize our sales and marketing efforts outside the United States, Canada and Mexico for Contrave, or with respect to Empatic depending on the terms of any collaboration agreement we may enter into for Empatic.

The Obesity Epidemic

Obesity is a serious condition that is growing in prevalence and afflicts populations worldwide. In 1980, approximately 15% of the adult population in the United States was obese, according to the National Health and Nutrition Examination Survey, or NHANES. By 2010, the obesity rate had more than doubled to approximately 36% of the U.S. population of adults over 20 years of age, according to the United States Centers for Disease Control and Prevention, or the CDC. According to a November 2009 report from the United Health Foundation, the American Public Health Association and Partnership for Prevention, it is estimated that by 2018, 43% of the U.S. adult population will be obese. In addition, obesity rates are projected to exceed 50% in 39 U.S. states by 2030, according to an October 2012 article in the Journal of the American Medical Association.

The growing prevalence of obesity has increasingly been recognized as a significant public health problem. The CDC has identified obesity as a chronic disease that is one of the leading causes of preventable deaths in the United States. Approximately 300,000 deaths per year in the United States are associated with obesity, according to the Department of Health and Human Services, or HHS. Obesity is also a significant health problem outside of the United States. According to the World Health Organization, there are as many as 1.5 billion people worldwide considered to be overweight, of whom at least 500 million are estimated to be obese.

Excessive body weight is also associated with various physical complications that are often present and exacerbated by the obese condition. Diabetes, cancer, hypertension, high cholesterol, coronary artery disease, sleep apnea, liver and pulmonary disease, among others, are seen in greater prevalence among the obese than the general population, according to HHS and The Obesity Society. Beyond these consequences, a number of co-morbidities involving the CNS may be complicated by obesity. These co-morbidities include anxiety, depression, substance abuse, chronic pain and insomnia. According to our market research, physicians in the United States report that approximately 63% of their obese patients have been diagnosed with depression or display signs and symptoms of untreated depression. We believe there is a growing recognition within the medical community that obesity significantly exacerbates these conditions and other co-morbidities.

Obesity and its co-morbidities are believed to cause significant added cost to the health care system. According to a January 2012 article in the Journal of Health Economics, annual U.S. obesity-related medical costs amount to an estimated $209.7 billion, which means that 20.6% of U.S. national health expenditures are spent treating obesity-related illness. A 2009 study examining the future impact of obesity on direct health care expenses projected these expenditures to increase to approximately $344 billion per year by 2018. Obesity has been linked to a more than one-quarter increase in health spending since the mid-1980s. We expect that more effective treatment of obesity may also be a cornerstone in managing its co-morbidities.

While there has been a broad recognition of obesity as a public health crisis, we believe that the obesity epidemic will continue to be a major cause of morbidity, mortality and excess health care costs in the United States. Despite the obesity rate, increasing public interest in the obesity epidemic and significant medical repercussions and economic costs associated with obesity, we believe there continues to be a need for more effective pharmacological interventions.

Limitations of Current Obesity Therapies

Treatments for obesity consist of behavioral modification, pharmaceutical therapies and surgical interventions including device implantation. Modifications to diet and exercise are the preferred initial treatment in obesity according to the National Institutes of Health. However, the rigors of behavioral modification often cause significant attrition over time and thus often results in regaining weight. When pharmaceutical therapies or surgical interventions are recommended, it is generally after behavioral modification alone has failed.

Bariatric surgery, including gastric bypass and gastric banding procedures, is employed in more extreme cases, typically for patients with a BMI exceeding 40. 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 patients with a BMI greater than 30 who are experiencing obesity related co-morbidities or patients with a BMI greater than 35 with or without obesity related co-morbidities. Surgery can be associated with significant side effects, potential complications including mortality, and substantial costs and recovery time. Certain device implantations used as therapies, such as neuromodulation, are not yet approved by the FDA.

Orlistat, phentermine, phentermine/topiramate, and lorcaserin are pharmaceutical products that have been approved for the treatment of obesity in the United States. Orlistat is marketed in the United States by Genentech, Inc. under the brand name Xenical ®, and is generally prescribed for short-term use. An extensive meta-analysis of various clinical trials published in the Annals of Internal Medicine in April 2005 reported that orlistat produces average weight loss of approximately 2.89 kg. Orlistat is associated with gastrointestinal side effects, the nature of which can be socially constraining, as evidenced in the FDA approved product information. These include flatulence, fecal incontinence and urgency. Orlistat was also launched in 2007 by GlaxoSmithKline in over-the-counter form at half the prescribed dose under the brand name allí ®. Phentermine is also generally prescribed for short-term use. Phentermine is a Schedule IV controlled substance and, according to the FDA-approved product information, has an amphetamine-like profile, an increased risk for abuse potential and may be associated with adverse cardiovascular or CNS effects. Vivus, Inc. commercially launched its combination phentermine/topiramate product in the United States under the name Qsymia™ in September 2012. In June 2012, Arena Pharmaceuticals, Inc., or Arena, obtained FDA approval for its product, lorcaserin, which it has indicated will be marketed, once launched, in the United States under the name Belviq™. Both of these drugs have an increased risk for abuse potential and therefore Qsymia has been, and Belviq has been proposed to be, designated as a Schedule IV controlled substance. The FDA also required a REMS for Qsymia to inform prescribers and women of reproductive potential about the increased risk of congenital malformation in infants exposed to Qsymia in early pregnancy. The Qsymia REMS program also requires that the drug is available only through certified mail order pharmacies.

Less than 2% of the obese population in the United States was treated with a pharmaceutical intervention in 2005, according to a September 2006 report by Frost & Sullivan. This represented approximately five million

total U.S. prescriptions, which we believe substantially understates the potential demand for effective treatments. By 2008, the number of total U.S. prescriptions for obesity products had increased to only approximately 7.8 million. In 2012, we conducted quantitative market research with 1,000 physicians, that suggests the U.S. market for obesity therapeutics could grow 3 to 4 fold within five years from a 2012 base of approximately 7.8 million prescriptions. We believe this history and research, combined with the substantial economic cost associated with obesity, underscores the unmet need and the potential for novel therapeutics to dramatically grow the market for obesity therapies.

The Orexigen Solution for Obesity

We believe and our research suggests that the CNS plays an important role in the regulation of appetite and energy expenditure. The brain, specifically the hypothalamus, plays a critical role in governing many fundamental processes throughout the body. The hypothalamus receives chemical and hormonal stimuli from various sources, including glucose, insulin, leptin and the peptides secreted by the gut as it processes food. These inputs govern a person's appetite, satiety and energy expenditure.

The brain contains numerous redundant circuits and compensatory mechanisms to preserve body weight, which should not be surprising given that maintenance of body weight is essential to survival. Such mechanisms are invoked in the presence of weight loss whether intentional (in the case of diet) or not (in the case of starvation). Moreover, in order to appropriately motivate humans to seek food, reward circuitries in the brain stimulate the urge to consume higher calorie food and in turn reward that behavior. The craving cycle is particularly intense with highly palatable foods, such as sweets.

Existing weight loss products that do not work by acting on the CNS cause some weight loss for most patients. We believe their modest effect stems from their failure to address these natural compensatory mechanisms in the body. As a result, most of these products have been vulnerable to a weight loss plateau typically seen after several months of therapy. In addition, they generally do not address the behavioral elements that contribute to unhealthy eating behaviors and, ultimately, obesity. We believe our product candidates sustain weight loss by preventing the body's natural tendency to counteract efforts to lose weight. In addition, with Contrave in particular, we are attempting to target the underlying behavioral mechanisms of craving and reward that drive excess consumption.

Our Product Candidates

Contrave

Contrave is a fixed dose combination of bupropion SR and naltrexone SR. We chose these constituents based on our understanding of the circuitries in the brain that regulate appetite and energy balance. In particular, naltrexone was chosen as a complement to bupropion in order to block compensating mechanisms that attempt to prevent long-term, sustained weight loss. We hold patents in the United States that cover the composition of Contrave (bupropion SR and naltrexone SR), as well as the use of Contrave for the treatment of obesity. We have also filed additional U.S. patents covering various aspects of Contrave. In addition, we own or have exclusive rights to numerous patent applications currently pending in various jurisdictions outside of the United States with respect to compositions, methods of use and formulations relating to Contrave.

Naltrexone was approved in the United States in 1984 for the treatment of opioid addiction and in 1994 for the treatment of alcoholism. It is marketed under the brand names Depade®, ReVia®, and in an injectable extended release formulation, Vivitrol®, which was approved in 2006 for the treatment of alcohol dependence and expanded in 2010 to include prevention of relapse to opioid dependence. Naltrexone immediate release formulation became available in generic form in the United States in 1998. Naltrexone works by blocking opioid receptors in the brain and inhibits the reinforcing aspects of addictive substances, reducing their perceived reward. Naltrexone was evaluated in the 1980s for weight loss and was shown to have negligible effects in clinical trials. Nausea is a well-known side effect associated with naltrexone immediate release that affects its

tolerability. In our Contrave Phase II clinical trials, we used the generic immediate release formulation of naltrexone. In our Phase III clinical trials, naltrexone was delivered in our proprietary SR formulation in order to improve its tolerability.

Bupropion was approved for marketing in the United States in 1985 for depression, marketed under the brand name Wellbutrin ®, and in 1997 for smoking cessation, marketed under the brand name Zyban ®. The immediate release version became available in generic form in the United States in 1999. Bupropion SR became available in generic form in the United States in 2004 and bupropion XL became available in generic form in the United States in December 2006. Bupropion is active at the neuronal uptake site for the neurotransmitters dopamine and norepinephrine. Functionally, bupropion is thought to increase the level of dopamine activity at specific receptors in the brain, which appears to lead to a reduction in appetite and increase in energy expenditure. In the 12-month period ending in August 2012, prescriptions of bupropion in the United States totaled approximately 26.6 million, according to IMS Health. Bupropion has become popular in the treatment of depression not only for its clinical efficacy, but also its attractive side effect profile relative to other antidepressants on the market. One of the reported side effects of bupropion in clinical trials for the treatment of depression was modest weight loss. Subsequently, bupropion has been studied for weight loss; results have shown approximately 3% placebo-corrected weight loss before reaching plateau, according to a study published in the October 2002 issue of Obesity Research.

Scientific Rationale

The two drug constituents of Contrave were chosen in order to leverage the brain's normal circuitry and biochemistry to reduce appetite, expend more calories, diminish food craving and food-based reward, and block compensating mechanisms that attempt to prevent long-term, sustained weight loss. Bupropion has been shown in studies to activate the proopiomelanocortin, or POMC, neurons within an area in the hypothalamus known as the arcuate nucleus. Increased firing of POMC neurons appears to lead to a reduction of appetite and an increase in energy expenditure. This is a major pathway by which naturally occurring peptides regulate body weight. Bupropion-induced stimulation of POMC activates this weight loss pathway.

Stimulation of POMC also produces beta-endorphin, an opioid occurring naturally in the body. Our early research identified a receptor on the POMC neuron that recognizes beta-endorphin. We discovered that by binding to this receptor, beta-endorphin serves as a brake on the POMC system. Left unchecked, this braking system acts to reduce POMC firing rates, thus moderating potential weight loss and likely explaining the characteristic plateau in weight loss. Based on this discovery, we chose naltrexone as the second component in Contrave. Naltrexone is a potent opioid receptor antagonist which competes with beta-endorphin, thus limiting its access at the receptor on the POMC neuron. When bupropion and naltrexone are co-administered, they both induce an increase in POMC firing that is maintained for an extended duration. This is expected to translate into a greater weight loss that should be sustained over an extended time period.

As a second benefit, both bupropion and naltrexone are known to act on the reward pathways in the brain that have been implicated in addiction to a number of substances, including food. These reward pathways are primarily regulated by dopamine and endogenous opioids, which are the targets of bupropion and naltrexone, respectively. Given that both drugs are approved for addiction-related disorders, we expect that together they may attenuate food craving and reward. As a result, we expect that Contrave may have an additional therapeutic benefit in patients who report food craving or obsession, which drives them to eat even when not hungry.

The COR Program

We have conducted controlled Phase II and Phase IIb clinical trials for Contrave in 657 patients. Based on the results of these trials, we concluded that Contrave showed sufficient efficacy as compared to each individual monotherapy and placebo and an acceptable safety and tolerability profile to warrant continued development in pivotal Phase III clinical trials.

Our Phase III program for Contrave was comprised of four distinct clinical trials that evaluated more than 4,500 patients. Based on our Phase II and Phase IIb trial results and feedback from the FDA, these four Phase III clinical trials in the COR program were designed to assess three doses of naltrexone SR (16mg, 32mg and 48mg) in combination with a 360mg dose of bupropion SR. All trials in the COR program were 56-week, randomized, double-blind, placebo-controlled trials.

The four Phase III clinical trials in the COR program are described as follows:

- COR-I (formerly NB-301): A trial designed to assess the safety, tolerability and efficacy of Contrave32 (32mg naltrexone SR plus 360mg bupropion SR) and Contrave16 (16mg naltrexone SR plus 360mg bupropion SR) versus placebo in 1,742 overweight/obese patients. This trial incorporated a typical diet and exercise regimen and was conducted across 34 U.S. centers.
- COR-II (formerly NB-303): A trial designed to assess the safety, tolerability and efficacy of Contrave32 versus placebo in 1,496 overweight/obese patients. This trial incorporated a typical diet and exercise regimen and was conducted across 36 U.S. centers. After week 28, patients not achieving 5% weight loss were re-randomized in a blinded fashion to assess whether increasing the dose to Contrave48 (48mg naltrexone SR plus 360mg bupropion SR) would result in additional weight loss.
- COR-Diabetes (formerly NB-304): A trial designed to assess the safety, tolerability and efficacy of Contrave32 versus placebo in 505 overweight/obese patients with Type 2 diabetes. This trial incorporated a typical diet and exercise regimen and was conducted across 53 U.S. centers.
- COR-BMOD (formerly NB-302): A trial designed to assess the safety, tolerability and efficacy of Contrave32 versus placebo in 793 overweight/obese patients in combination with an intensive behavior modification protocol, including dietary counseling, behavioral therapy and exercise. This trial was conducted across nine U.S. centers. This trial included the most intensive behavior modification regimen of the COR program, which resulted, as expected, in a high degree of weight loss among placebo patients.

The co-primary endpoints for all four clinical trials in the COR program were the proportion of patients achieving at least 5% weight loss and percent change in body weight compared to placebo. The co-primary endpoints for COR-I, COR-Diabetes and COR-BMOD were all measured at 56 weeks. The co-primary endpoints for COR-II were measured at 28 weeks. These endpoints were analyzed using a modified intent-to-treat, or ITT, last observation carried forward on treatment, or LOCF, of all randomized patients who had at least one post-baseline observation while on study drug. Contrave was administered twice a day with a four week titration period in COR-I, COR-Diabetes and COR-BMOD. Contrave was administered twice a day with a five week titration period in COR-II. All four clinical trials met their co-primary endpoints.

The 56-week results for all four clinical trials in the COR program are as follows:

	COR-I			
	ITT 56 weeks		Completers† 56 weeks	
	Contrave32 (n=471)	Placebo (n=511)	Contrave32 (n=296)	Placebo (n=290)
Mean Weight Loss (%)	6.1%*	1.3%	8.1%*	1.8%
Mean Weight Loss (lbs)	13.3*	3.0	17.5*	4.1
Greater than or equal to 5% weight loss (%)	48.0%*	16.4%	61.8%*	23.1%
Greater than or equal to 10% weight loss (%)	24.6%*	7.4%	34.5%*	10.7%

* Difference from placebo, p<0.001

† Those patients completing 56 weeks of treatment.

ITT, LOCF patients administered Contrave16 (n=471) experienced mean weight loss from baseline of 5.0% at 56 weeks; 39.5% of patients lost greater than or equal to 5% of their body weight at 56 weeks and 20.2% of patients lost greater than or equal to 10% of their body weight at 56 weeks.

	COR-II			
	ITT†		Completers**	
	56 weeks‡		56 weeks‡	
	Contrave32 (n=702)	Placebo (n=456)	Contrave32 (n=434)	Placebo (n=267)
Mean Weight Loss (%)	6.4%*	1.2%	8.2%*	1.4%
Mean Weight Loss (lbs)	13.8*	2.9	17.5*	3.4
Greater than or equal to 5% weight loss (%)	50.5%*	17.1%	64.9%*	21.7%
Greater than or equal to 10% weight loss (%)	28.3%*	5.7%	39.4%*	7.9%

† Co-primary endpoints for COR-II were the proportion of patients achieving at least 5% weight loss and percent change in body weight compared to placebo at 28 weeks. ITT patients (n=1,281) at 28 weeks experienced mean weight loss from baseline of 6.5% versus 1.9% for placebo; 55.6% of patients lost greater than or equal to 5% of their body weight at 28 weeks versus 17.5% for placebo and 27.3% of patients lost greater than or equal to 10% of their body weight at 28 weeks versus 7.0% for placebo.

** Those patients completing 56 weeks of treatment.

‡ Pre-specified exploratory analysis; Contrave32 patients not achieving 5% weight loss double weighted because Contrave 48 patients were excluded from efficacy analysis. There was no statistical difference between patients re-randomized to Contrave32 or Contrave48.

* Difference from placebo, p<0.001

	COR-BMOD			
	ITT		Completers†	
	56 weeks		56 weeks	
	Contrave32 (n=482)	Placebo (n=193)	Contrave32 (n=301)	Placebo (n=106)
Mean Weight Loss (%)	9.3%*	5.1%	11.5%*	7.3%
Mean Weight Loss (lbs)	20.3*	11.0	25.0*	16.0
Greater than or equal to 5% weight loss (%)	66.4%*	42.5%	80.4%*	60.4%
Greater than or equal to 10% weight loss (%)	41.5%*	20.2%	55.2%*	30.2%

* Difference from placebo, p<0.001

† Those patients completing 56 weeks of treatment.

	COR-DIABETES			
	ITT		Completers†	
	56 weeks		56 weeks	
	Contrave32 (n=265)	Placebo (n=159)	Contrave32 (n=175)	Placebo (n=100)
Mean Weight Loss (%)	5.0%*	1.8%	5.9%*	2.2%
Mean Weight Loss (lbs)	11.6*	4.2	13.5*	5.1
Greater than or equal to 5% weight loss (%)	44.5%*	18.9%	53.1%*	24.0%
Greater than or equal to 10% weight loss (%)	18.5%*	5.7%	26.3%*	8.0%

* Difference from placebo, p<0.001

† Those patients completing 56 weeks of treatment.

Secondary endpoints included multiple measures of cardiometabolic risk, food cravings and eating control. Measures of hemoglobin A1c, or HbA1c, and other measures of glycemic control were also key secondary endpoints in the COR-Diabetes trial. Secondary endpoints that demonstrated clinically and statistically

significant improvements over placebo across the entire COR program included cardiometabolic risk factors such as waist circumference, HDL cholesterol and triglycerides. Patients enrolled in the COR program also experienced reductions in the frequency and strength of food cravings and an increased ability to control their eating compared to placebo. In the COR-Diabetes trial, patients administered Contrave showed a reduction in HbA1c of 0.6% from baseline, compared to a 0.1% reduction in placebo.

The overall discontinuation rates across the COR program ranged from 42% to 51% for the Contrave treated groups compared to 41% to 50% for the placebo groups. The discontinuation rates due to adverse events across the COR program ranged from 19% to 29% for the Contrave treated groups compared to 10% to 15% for the placebo groups. The most frequent adverse events leading to discontinuation for patients taking Contrave were nausea, headache, vomiting and dizziness. Nausea was the leading adverse event resulting in discontinuation; however, for the majority of patients experiencing nausea, it was mild to moderate, transient and manageable. The most frequently observed treatment-emergent adverse events were nausea, constipation and headache. Across the entire COR program, seven serious adverse events were attributed by investigators as possibly related to Contrave treatment. These included cholecystitis (gallbladder inflammation) (2), seizure (2), palpitations (1), paresthesia (1) and vertigo (1). In addition, there was one death of a patient on Contrave that was not attributed by investigators as related to Contrave treatment, but rather was attributed to a cardiovascular serious adverse event. At week 56, mean blood pressure was generally unchanged from baseline for Contrave patients, compared to placebo patients who tended to experience a slight decrease (approximately 2 mm Hg) from baseline. Contrave treatment did not appear to disrupt the normal circadian pattern of blood pressure. There was a slight increase in pulse (approximately 1 beat per minute) in Contrave patients, compared to placebo patients whose pulse was generally unchanged. There were no meaningful treatment effects on ECGs or laboratory measures including liver function tests. Treatment with Contrave was not associated with increases in symptoms of depression or suicidal ideation.

We believe that our clinical trial experience with Contrave has demonstrated and replicated the validity of our naltrexone hypothesis, specifically, that the addition of naltrexone to bupropion permits greater weight loss than bupropion alone and sustains weight loss beyond 24 weeks. Moreover, in our Phase II clinical trials, Contrave has demonstrated significantly greater weight loss than naltrexone alone as well as placebo. The rate of response (greater than 5% and 10% reduction in body weight from baseline) has also favored Contrave and provides additional support for our belief that Contrave will provide a clinically relevant alternative for clinicians and obese patients. We believe the results from the COR program exceed the FDA categorical efficacy benchmark for clinically significant weight loss.

Open-Label Study for Smoking Cessation. We have conducted an exploratory, open-label 24-week clinical trial of Contrave32 for smoking cessation in overweight or obese patients. This trial was conducted in 30 patients across three U.S. centers. The primary endpoint for this trial was the rate of smoking cessation as defined by patient-reported continuous abstinence during weeks 4-12. Secondary endpoints, which were measured at Week 12 and 24, included: rate of smoking cessation as defined by patient-reported continuous abstinence during weeks 4-24; percent change from baseline in total body weight; and a number of other key measures. Additionally, measures of safety and tolerability were evaluated. The endpoints were analyzed using ITT, LOCF.

In this trial, Contrave32 significantly reduced cigarette use among obese patients trying to quit smoking and was not associated with clinically meaningful weight gain. The smoking cessation rates as measured by patient-reported continuous abstinence were 48.1% and 40.7% at Week 12 and 24, respectively. Improvements were also seen in a number of key secondary endpoints. The most frequent adverse events were nausea, insomnia and constipation. These tended to be transient and mild or moderate in severity. No serious adverse events occurred. Five patients withdrew from this trial due to adverse events.

Open-Label Study for Obese Depressed Patients. We have conducted an exploratory, open-label 24-week clinical trial assessing the safety and efficacy of Contrave32 in overweight or obese patients with major depression. This trial was a single-center trial conducted in 25 patients. The primary endpoint for this trial was the change from baseline in the Montgomery-Asberg Depression Rating Scale, or MADRS, total score at Week

12. Secondary endpoints included change from baseline in the MADRS total score at Week 24, as well a number of other key measures. Additionally, measures of safety and tolerability were evaluated. The endpoints were analyzed using ITT, LOCF.

In this trial, Contrave32 showed a clinically significant reduction in depressive symptoms in the study population, as evidenced by mean decreases from baseline in MADRS total scores of more than 50% at Weeks 12 and 24. Improvements were also seen in a number of key secondary endpoints. The most frequent adverse events were nausea, constipation, headache and insomnia. These adverse events tended to be moderate in severity. No serious adverse events occurred during the trial that were attributed to treatment with Contrave32. Ten patients withdrew from the trial due to adverse events.

The Light Study. We submitted the Contrave NDA to the FDA in March 2010. In January 2011, we received a CRL from the FDA regarding our NDA for Contrave. The CRL for Contrave indicated that the FDA could not approve the NDA in its present form primarily due to concerns regarding the cardiovascular safety profile of Contrave when used long-term in a population of overweight and obese subjects. The CRL stated that before our NDA could be approved, we must conduct a randomized, double-blind, placebo-controlled trial of sufficient size and duration to demonstrate that the risk of MACE in overweight and obese patients treated with Contrave does not adversely affect the drug's benefit-risk profile. In September 2011, we received written correspondence detailing the OND's design requirements for a CVOT for Contrave that would address the CRL. Importantly, the FDA stated that if the interim analysis meets the specified criteria to exclude an unacceptable increased cardiovascular risk, the drug could be approved prior to completion of the CVOT. If the interim analysis excludes a doubling of risk of MACE in patients receiving Contrave compared to placebo, we plan to resubmit the Contrave NDA to the FDA for approval. The exclusion of a doubling of risk of MACE was established as the threshold for approvability of Contrave during discussions with the FDA prior to the start of the Light Study. An interim analysis is planned once the Light Study's independent Data Monitoring Committee has determined that sufficient information has been gathered for the analysis that would include at least 87 adjudicated MACE. In February 2012, we reached agreement with the FDA on the SPA for the CVOT. We initiated the Light Study in June 2012.

The Light Study is a randomized, double-blind, placebo-controlled cardiovascular outcomes trial that is being conducted at approximately 265 sites in the United States. The primary objective of the Light Study is to assess Contrave (32 mg naltrexone sustained-release (SR)/360 mg bupropion SR (NB32)) compared to placebo on the occurrence of MACE (cardiovascular death, nonfatal myocardial infarction or nonfatal stroke) in overweight and obese patients. Of note, weight loss is not a primary or secondary objective of the Light Study as it is primarily a safety trial and the efficacy benchmark has already been established as acceptable from our Phase III COR program. After a double-blind lead-in period was conducted to exclude patients who exhibit characteristics predictive of lack of compliance or who do not tolerate treatment with Contrave well, approximately 8,900 eligible patients were randomized with either Contrave or placebo in a 1:1 ratio. The duration of the randomized treatment period (or patient follow-up period for those who discontinue study drug early) is estimated to be between 2-4 years for most patients. The estimated average duration of blinded study drug exposure is approximately 4-6 months at the time of the interim analysis depending on when the interim analysis occurs and 1.4 years at the time of the final analysis.

All patients, regardless of randomized treatment assignment, will participate in a weight management program tailored for the Light Study. We believe this is a significant value proposition to enhance retention in the Light Study. At week 16 there will be an evaluation of weight loss relative to baseline observations. At that time, patients will be discontinued from study drug if they have not lost at least 2% of their body weight or if they have sustained (e.g., at 2 or more visits) increases in blood pressure (systolic or diastolic) of 10 mm Hg or greater, so only appropriate responders move forward on study drug after week 16. The Light Study is a large but streamlined trial without frequent site visits or intensive data collection, such as on-trial blood draws. Every two months between visits beyond week 26, patients will be asked to answer specific questions pertaining to compliance and hospitalizations (potential MACE or serious adverse events), using an internet- or telephone-based data collection system.

In October 2012, we announced that we received a response to a formal dispute resolution request from CDER. We had requested that Contrave be considered for approval on the basis of existing data together with a postmarketing requirement to supply the interim analysis of the Light Study shortly after approval. CDER denied this request, reaffirming that the cardiovascular outcomes data from the interim analysis of the Light Study is required prior to approval; however, CDER indicated that it was highly supportive of the exploration of a faster path to resubmission of the Contrave NDA. In January 2013, the FDA's DMEP proposed a resubmission procedure that would allow the independent Data Monitoring Committee's summary report of the Light Study interim analysis to form the basis of the resubmission of the Contrave NDA. The complete clinical study report, or CSR, for the interim analysis, which would ordinarily form the basis for the NDA resubmission filing, would be provided to the FDA during its review of the NDA within 60 days of the NDA resubmission. If marketing approval is received for Contrave, the Light Study will continue toward the final analysis in the post-approval setting.

We enrolled a patient population that we predicted would have an annualized MACE rate between 1% and 2%. The demographics (age, gender, smoking status, prevalence of cardiovascular disease, diabetes and other co-morbidities) of the patients randomized into the Light Study to date are in line with the targeted population. In this population, the upper bound of the 95% confidence interval should exclude a hazard ratio of 2.0 and 1.4 at the interim and final analyses, respectively.

The timing of the interim analysis and the Contrave NDA resubmission is dependent on the timing of MACE observed in the Light Study. The observed MACE rate may differ materially from modeled MACE rate. We are preparing to be ready to conduct the interim analysis and resubmit the Contrave NDA in 2013. However, if the observed MACE rate is at or near the low end of the targeted range of 1% to 2%, the resubmission of the Contrave NDA may not occur until early 2014.

The final analysis will be conducted once at least 371 MACE events are adjudicated. The primary endpoint of MACE will be analyzed using the intent-to-treat population. An on-treatment analysis using the per protocol population will be conducted as a sensitivity analysis.

The Ignite Study. In February 2013, we commenced the Ignite Study, a randomized, open-label clinical trial of 242 patients. The Ignite Study is designed to provide additional information regarding the real world weight loss potential of Contrave in combination with a commercially available comprehensive lifestyle intervention program, compared to patients who receive diet and exercise advice from the study site staff but who do not receive Contrave. Consistent with current labeling for recently approved anti-obesity medications, patients in the Ignite Study must achieve a certain amount of weight loss (5% at week 16) and must not have a meaningful increase in blood pressure to remain on medication. The primary endpoint for this trial is change in body weight after 26 weeks. Secondary endpoints include the percentage of patients achieving 5% and 10% weight loss, waist circumference, lipids, and measures of glucose homeostasis, as well as a number of other key measures. The primary analysis population is the 26-week per-protocol population.

European Marketing Authorization Application. We have initiated activities with the European Medicines Agency, or EMA, to enable submission of a Community Marketing Authorization, or Community MA, application supporting potential approval of Contrave in the European Economic Area, or EEA (which is comprised of the 27 Member States of the European Union plus Norway, Iceland and Liechtenstein), under the centralized procedure. The centralized procedure, for which Contrave is eligible, allows for the simultaneous approval of a product in all the Member States of the EEA. A Community MA application is reviewed by the EMA's Committee for Medicinal Products for Human Use, or CHMP. After submission and validation of the Community MA application, the CHMP generally has 210 days to complete its assessment and adopt an opinion on whether or not to recommend the granting of the Community MA. The 210 days period does not include the anticipated "clock stops" at specified points in the procedure, typically at day 120 (Consolidated List of Questions) and at day 180 (List of Outstanding Issues). The clock stops allow time for us to address the

outstanding questions or issues raised by the CHMP. At day 180, depending on the List of Outstanding Issues, an oral hearing with the CHMP may be required to address specific issues. Assuming a positive opinion from the CHMP, a final Community MA is granted by the European Commission on day 277 of the procedure, not counting clock stops as noted above. We expect to submit the Contrave Community MA around the time of the resubmission of the Contrave NDA. As a result, we are also in the process of establishing an agreed-to pediatric investigation plan, or PIP, with the EMA's Pediatric Committee. An agreed PIP is required before submitting the Community MA application.

Empatic

Empatic is a fixed dose combination of bupropion SR and zonisamide SR. The combination of bupropion and zonisamide, in our screening model, suggested a synergistic increase in POMC neuronal firing, indicating that this drug combination would enhance satiety and energy expenditure. We have also validated this synergy in rodent models of obesity. Based on the strength of these results we selected this product combination to complement our Contrave clinical development program. We hold an exclusive license to an issued U.S. patent covering the Empatic composition and methods of use in obesity, and we have filed additional patents covering various compositions, methods of use and formulations.

Zonisamide immediate release was approved in the United States in 2000 for the adjunctive treatment of partial seizures, a form of epilepsy. It is marketed under the brand name Zonegran® by Eisai Inc., which acquired the rights to the product from Elan Pharmaceuticals in 2004. Zonegran became available in generic form in the United States in 2005, and at its peak produced approximately $177 million in annual sales, according to IMS Health. The precise mechanism of zonisamide is unknown; however, it is believed that zonisamide has a number of pharmacologic mechanisms including sodium-channel modulation and enhancement of dopamine and serotonin neurotransmission. Zonisamide, given alone, has also shown weight loss in prior clinical trials conducted at Duke University, or Duke.

Scientific Rationale

Like Contrave, Empatic employs bupropion to stimulate POMC. The second component in Empatic, zonisamide, has been shown in our research to increase the firing rate of POMC neurons by up to eightfold in the presence of bupropion. We also believe that zonisamide may have one or more additional effects. Within the hypothalamus, a set of neurons acts in a reciprocal way to POMC. These are referred to as the Neuropeptide Y/Agouti-related peptide, or NPY/AgRP, neurons. Stimulation of NPY/AgRP neurons results in the release of AgRP, which binds to the melanocortin-4, or MC-4, receptor, resulting in an increase in appetite and energy conservation. The pharmacology of zonisamide has been hypothesized to also inhibit the firing of NPY/AgRP neurons. Strategies that minimize AgRP competition for the MC-4 receptor thus may have the potential to lead to substantive weight loss.

Empatic Clinical Results

Phase IIb Clinical Trial (ZB-201). Based on the results of an initial Phase II proof-of-concept clinical trial for Empatic that enrolled 127 patients across five U.S. centers, we concluded that Empatic showed sufficient efficacy and an acceptable safety and tolerability profile to warrant continued development. In June 2006, we proceeded to study Empatic in a larger randomized, double-blind, placebo-controlled Phase IIb clinical trial exploring several different dosage combinations of bupropion and zonisamide in 623 patients with a BMI between 30 and 43 across 15 U.S. centers.

The primary endpoint for this trial was percent change in body weight measured 24 weeks after the start of treatment. Data were analyzed using ITT, LOCF. For the ITT population, the mean weight loss at 24 weeks ranged from 4.5% of body weight for the lowest dosage tested to 8.6% for the highest dosage tested, versus 1.1% for placebo. Based on these results, as well as the fact that Empatic appeared safe and generally well tolerated, we decided to take two dosages into further clinical testing.

Additional Phase IIb Clinical Trial (ZB-202). We submitted to the FDA the results of the initial Phase IIb clinical trial (ZB-201) at 24 weeks, the primary endpoint. In subsequent correspondence, the FDA confirmed the design of our next Phase IIb clinical trial. We announced the results of this trial in September 2009. This trial was designed to evaluate Empatic at two different dosages (based on the results of our initial Phase IIb clinical trial (ZB-201)) against the individual monotherapies and placebo.

This 24-week, double-blind, placebo-controlled, randomized trial evaluated 729 patients across 20 U.S. centers and incorporated a typical diet and exercise regimen. Patients enrolled in this trial had a BMI between 30 and 45, or as low as 27 in the presence of controlled hypertension or dyslipidemia. The trial studied six arms: placebo, one dose of bupropion monotherapy, two doses of zonisamide monotherapy and two doses of Empatic (360 mg zonisamide SR and 360 mg bupropion SR, or Empatic360/360; and 120 mg of zonisamide SR and 360 mg of bupropion SR, or Empatic120/360).

The primary objective of this trial was to show greater weight loss with Empatic compared to its individual monotherapies and placebo, in accordance with the FDA guidance for combination products. Data were analyzed using ITT, LOCF. This Phase IIb clinical trial met its primary efficacy endpoint by demonstrating statistically significantly greater weight loss for both Empatic doses compared to monotherapies and placebo. Results showed mean weight loss for Empatic360/360 was 7.5% of body weight versus 1.4% for placebo, 2.3% for bupropion 360 and 5.3% for zonisamide 360. Mean weight loss for Empatic120/360 was 6.1% of body weight versus 1.4% for placebo, 2.3% for bupropion 360 and 3.2% for zonisamide 120. For the completer population, the mean weight loss at 24 weeks was 9.9% for Empatic360/360 and 7.7% for Empatic120/360 versus 1.7% for placebo.

The overall discontinuation rates for patients treated with Empatic360/360 and Empatic120/360 were 40.2% and 41.9%, respectively, compared to 40.4% for the placebo group. The discontinuation rates due to adverse events for patients treated with Empatic360/360 and Empatic120/360 was 23.4% and 24.7%, respectively, compared to 13.5% for the placebo group. The most frequent adverse events, as well as those resulting in discontinuation, were headache, nausea and insomnia. Adverse events and laboratory findings appeared to be consistent with the individual components of Empatic. Specifically, infrequent reports of idiopathic neutropenia, or transient extremely low white blood cell counts, were observed. Sulfonamides, of which zonisamide belongs, are one of many classes of drugs which have been reported to infrequently cause benign idiopathic neutropenia. There were no serious adverse events attributed by investigators to study drug. There were no statistically or clinically meaningful differences between Empatic and placebo on measures of cognitive function, depression, suicidality or anxiety.

In our recent series of discussions with the FDA on the continued development of Empatic, the FDA stated that Phase III data for Empatic may be sufficient to support submission of an NDA without data from a cardiovascular outcomes trial. The FDA indicated that as long as the placebo-subtracted changes in body weight, blood pressure and heart rate for Empatic are similar to or more favorable than the placebo-subtracted changes observed with Contrave, and there are no signals of cardiovascular concern in the Empatic development program, reassuring results of a cardiovascular outcomes trial with Contrave will be sufficient. In addition, while the FDA reiterated its belief that the preclinical teratogenicity data for zonisamide and the pregnancy outcome data with Empatic from our Phase II clinical trials are very concerning, it will allow Phase III studies of Empatic to include women of childbearing potential with a BMI >27kg/m^2 in the presence of at least one weight-related comorbidity such as hypertension, type 2 diabetes mellitus or dyslipidemia and a BMI >30 kg/m^2 without additional restrictions if appropriate safety measures and adequate informed consent are provided. The FDA noted that similar safety measures and understanding of risk in the Phase III trials may need to be applied in the intended marketed population if Empatic is approved. The FDA added that additional worrisome pregnancy outcome data in the Empatic trials may have an impact on approvability, labeling or REMS. Prior to initiating Phase III studies of Empatic, we plan to seek a collaboration partner to help fund clinical development of and, if approved, commercialization of Empatic.

We are following the commercial progress in the United States and the regulatory progress in the European Union of Vivus' phentermine/topiramate product for the treatment of obesity, which also contains an

anti-convulsant. We believe the commercial success in the United States and the regulatory outcome and potential labeling in the European Union will inform the development path and commercial prospects for Empatic. For example, although Vivus obtained FDA approval for phentermine/topiramate, in October 2012 the CHMP adopted an opinion recommending against the approval of the marketing authorization application for such product due to concerns about its long-term effects on the heart and blood vessels, particularly due to the effects of the phentermine component, its long-term psychiatric effects (depression and anxiety were reported in the studies) and cognitive effects (such as problems with memory and attention) related to the topiramate component, as well as known risks with topiramate being potentially harmful to the unborn baby if taken by pregnant women. The CHMP also noted that there was a high probability that, if approved, Vivus' product would not be used strictly for the intended patients. Vivus requested a re-examination of the CHMP's opinion. After considering the grounds for this request, the CHMP re-examined the initial opinion, and confirmed the refusal of the marketing authorization in February 2013. Further, according to Vivus, the CHMP indicated that a pre-approval CVOT would be necessary to establish the long-term safety of its product. We may face similar negative recommendations with respect to any regulatory filings we submit for our product candidates in the European Union and other geographies.

Sales and Marketing

We are developing our product candidates for large markets traditionally served by primary care physicians. In order to effectively promote Contrave to these physicians, in September 2010, we entered into a collaboration agreement with Takeda to develop and commercialize Contrave in the United States, Canada and Mexico. Subject to certain terms and conditions, the collaboration agreement allows us to co-promote Contrave in the United States. We currently retain marketing rights for Contrave outside the United States, Canada and Mexico and worldwide marketing rights for Empatic. We may consider entering into additional collaborations with other pharmaceutical companies for territories outside the United States, Canada and Mexico with the sales force and marketing resources to adequately address the large primary care physician audience. Prior to initiating Phase III studies of Empatic, we plan to seek a collaboration partner to help fund clinical development of and, if approved, commercialization of Empatic. We may also consider utilizing the resources of a contract sales organization or other third-party vendor to optimize our sales and marketing efforts outside the United States, Canada and Mexico for Contrave, or with respect to Empatic depending on the terms of any collaboration agreement we may enter into for Empatic.

Intellectual Property

We rely on a combination of in-licensed patent rights, our own patent rights, trademarks, trade secrets and know-how to protect Contrave and Empatic. We own or have exclusive rights to several patent application families currently pending in the United States with respect to various compositions, methods of use and formulations relating to Contrave and/or Empatic. We also have a number of patent applications currently pending in various foreign countries that correspond to some of the pending U.S. applications. We also seek to protect our trade secrets and our know-how relating to our products and our business. These intellectual property rights are in addition to any regulatory exclusivity that we may be able to obtain.

Contrave is currently protected, in part, by U.S. patent number 5,512,593 issued in April 1996 and U.S. patent number 5,817,665 issued in October 1998, which we have licensed on an exclusive basis from Dr. Lee Dante pursuant to a license agreement described in further detail below and which we collectively refer to as the Dante patents. Provided maintenance fees are paid, U.S. patent number 5,512,593 is expected to expire in April 2013 and U.S. patent number 5,817,665 is expected to expire in March 2013. The Dante patents do not protect Contrave outside of the United States. The Dante patents cover compositions of certain specified opioid antagonists (including naltrexone) combined with certain specified antidepressants (including bupropion), and thus provide coverage for Contrave.

In addition to the Dante patents, Contrave is also currently protected by U.S. patent number 7,375,111, which we refer to as the Weber/Cowley composition patent, and U.S. patent number 7,462,626, which we refer to

as the Weber/Cowley methods patent. Provided maintenance fees are paid, the Weber/Cowley composition patent is expected to expire in March 2025, and the Weber/Cowley methods patent is expected to expire in July 2024. Collectively, we refer to the Weber/Cowley composition patent and the Weber/Cowley methods patent as the Weber/Cowley patents. Each of these stems from a provisional patent application that we own but that is the subject of agreements with the Oregon Heath & Science University, or OHSU, and Duke requiring us to pay them specified royalties on sales of products covered by the patent applications. These agreements are described in further detail below. The Weber/Cowley patents cover the current composition of Contrave and methods of administering it to treat obesity. We have also filed a number of international counterparts to these patent applications in foreign countries. The European Patent Office, or EPO, has granted the European version of the Weber/Cowley patent, which published as EP1617832 B1. This EP patent has issued in numerous countries throughout the European Union and provides coverage for Contrave until at least 2024. Additional patent applications related to Contrave remain pending in the U.S. and throughout the world.

We have also filed patent applications in the United States and certain foreign countries under the Patent Cooperation Treaty, or PCT, which is an international treaty providing a unified procedure under which the initial filing of a single patent application can provide an effective filing date in each participating country in which appropriate steps are subsequently taken. Such steps have been taken in various foreign countries, including countries in Europe and Japan, with respect to our PCT filings directed to various treatment and formulation aspects of Contrave. Thus, we now have patent applications pending in those countries (along with our previous filings in the United States and certain non-PCT countries) that seek to provide further protection for Contrave. However, we cannot provide assurance that the claims in these patent applications will issue in their current form or at all.

We have received U.S. trademark registration number 3393576 for the mark CONTRAVE for use in connection with pharmaceutical preparations for use in the treatment of obesity and inducing weight loss. An application for the CONTRAVE mark has been allowed in the United States in connection with certain printed materials and medical information services. We have also obtained foreign trademark registrations for the mark CONTRAVE in Canada, Europe and Japan. In addition, applications for a Contrave logo for use in connection with pharmaceutical preparations for use in the treatment of obesity and inducing weight loss, certain printed materials and medical information services has been allowed in the U.S., and is pending in Canada. The Contrave logo is also registered in Europe and Japan.

Empatic is currently protected in the United States by U.S. Patent Number 7,109,198, which is based on the work of Dr. Kishore Gadde, and which we refer to as the Gadde patent and have licensed on an exclusive basis from Duke pursuant to a patent license described in further detail below. The Gadde patent, which is expected to expire in 2023, provides basic composition of matter coverage for the Empatic zonisamide/bupropion combination and also covers methods of using Empatic to treat obesity and to reduce the risk of hypertension, diabetes or dyslipidemia. A continuation patent application, related to the Gadde patent and also exclusively licensed to us, issued as U.S. Patent Number 7,425,571. This patent covers methods of using zonisamide (including in combination with bupropion) to cause weight loss, and provides additional coverage for methods of using Empatic to treat obesity until 2023. We have also exclusively licensed from Duke an international patent application that was filed as a counterpart to the Gadde patent in foreign countries, and this international application has now matured into national applications pending in several foreign countries. Our filings directed to formulations and use of SR zonisamide, an ingredient in Empatic, include U.S. patent number 7,754,748, which issued in July 2010, and pending patent application in certain non-PCT countries, Europe and Japan. These filings seek to provide additional protection for Empatic, but we cannot provide assurance that the claims in these patent applications will issue in their current form or at all. We have received a Notice of Allowance from the U.S. Patent and Trademark Office for the intent-to-use trademark application for the mark EMPATIC for use in connection with pharmaceutical preparations for the treatment of obesity and inducing weight loss, various printed materials, and medical information services. Foreign trademark registrations have issued in Europe and Japan for the mark EMPATIC, and an application remains pending in Canada.

We have received U.S. trademark registration number 3396021 for our corporate logo for use in connection with pharmaceutical preparations and substances for the treatment of obesity, inducement of weight loss and prevention of weight gain. We have obtained trademark registrations in Canada, Europe and Japan for the same mark. In addition, we have received U.S. trademark registration number 3396807 for our corporate name OREXIGEN for use in connection with pharmaceutical preparations for the treatment of disorders of the CNS, printed instructional, educational and teaching materials in the field of treatment and management of disorders of the CNS, and providing medical information in the field of disorders of the CNS. We have obtained trademark registrations in Canada, Europe and Japan for the same mark. We have obtained foreign trademark registrations for the corporate name Orexigen Therapeutics, Inc. in Europe and Japan.

Collaboration and Licensing Agreements

Collaboration Agreement with Takeda Pharmaceutical Company Limited

In September 2010, we entered into a collaboration agreement with Takeda to develop and commercialize Contrave in the United States, Canada and Mexico. Under the terms of the collaboration agreement, we received an upfront cash payment of $50 million from Takeda, and we are eligible to receive additional payments of over $1 billion upon achieving certain anniversary, regulatory and sales-based milestones, including $100 million that can be achieved between regulatory approval and the first commercial sale of Contrave in the United States, Canada and Mexico and $45 million in anniversary milestones. We are also eligible to receive tiered royalty payments ranging from a minimum of 20% to a maximum of 35%, subject to customary reductions, on increasing levels of net sales in the United States, Canada and Mexico.

The collaboration agreement provides that Takeda will be responsible for commercialization costs and activities. Takeda has agreed to use commercially reasonable efforts in commercializing Contrave in the United States, Canada and Mexico in addition to specified commercial diligence commitments in the first three years in the United States after product launch, if at all. Subject to certain terms and conditions, the collaboration agreement also allows us to co-promote Contrave in the United States and, subject to certain limitations, Takeda shall be responsible for certain commercialization costs associated with our co-promote sales force.

We will bear all costs and be responsible for development activities conducted prior to approval of the NDA for Contrave by the FDA. Both parties will conduct development activities after NDA approval; however, we have the right to perform a certain percentage of such activities. Once we have paid for $60 million of post-approval development activities, Takeda will generally be responsible for 75% of the post-approval development costs and we will be responsible for 25% of such costs, except for certain clinical safety trial costs for which we will be responsible for 50% of such costs.

As a part of the collaboration agreement, Takeda has committed to purchase its requirements of Contrave from us. However, at any time during the term of the collaboration agreement, Takeda may elect, subject to certain terms and conditions, to transfer and assume the right and responsibility to manufacture Contrave in the United States, Canada and Mexico.

Both parties have agreed not to commercialize any other pharmaceutical product for the treatment of obesity or weight management through a specified date, other than Contrave and any product owned or controlled by either party as of the date of the collaboration agreement.

Unless earlier terminated, the term of the collaboration agreement shall expire on the first to occur of (1) on a country-by-country and product-by-product basis, upon the expiration of the specified royalty term in such country; or (2) in its entirety upon the expiration of the specified royalty term in all countries with respect to the last product covered under the agreement commercialized in such countries. Takeda has the right to terminate the agreement upon specified prior written notice. In addition, both parties have certain termination rights in the circumstance of unexpected product safety issues, and Takeda has certain termination rights in the circumstance

of pre-specified post-approval regulatory requirements. Both parties may terminate the agreement immediately for insolvency of the other party, in the case of a patent challenge by the other party, and, upon certain specified notice, for uncured material breach of terms and conditions of the collaboration agreement.

Oregon Health & Science University License Agreement

In June 2003, we entered into a license agreement with OHSU whereby we acquired an assignment of any rights OHSU may have to a U.S. provisional patent application that we filed, which formed the basis for the Weber/Cowley patents. These patents, as discussed above, cover the current composition of Contrave, including our SR formulation of naltrexone and methods for using that composition to effect weight loss. OHSU and the inventors have assigned all rights in the underlying invention to us. This license agreement was amended in November 2003, December 2006 and December 2007.

As consideration for this license agreement, we paid an upfront fee of $65,000 and issued 76,315 shares of our common stock to OHSU. We are also obligated to pay a royalty to OHSU on net sales for Contrave and any other products covered by the assigned patent rights.

The term of the agreement generally extends until the last of the subject patent rights expire, which is expected to occur in 2025. We may unilaterally terminate the agreement and/or any licenses in any country upon specified written notice to OHSU. OHSU may terminate the agreement upon delivery of written notice if we commit a material breach of our obligations and fail to remedy the breach within a specified period or may immediately terminate the agreement upon the delivery of written notice concerning the occurrence of specified bankruptcy proceedings. In addition, upon written notice and our failure to remedy any of the following breaches within a specified period, OHSU may terminate or modify the agreement: if we cannot demonstrate to OHSU's satisfaction that we have taken, or can be expected to take within a reasonable time, effective steps to achieve practical application of the licensed products and/or licensed processes; or if we have willfully made a false statement of, or willfully omitted, a material fact in any report required by the agreement; or if we commit a substantial breach of a covenant or agreement contained in the license. Under the terms of the agreement, we are responsible for all prosecution and maintenance (including all costs associated with the enforcement) of any patent applications that stem from the assigned rights, and for any patents that have or may issue with respect thereto, including the Weber/Cowley patents.

In addition to assigning us any rights it had in our provisional patent application directed to the Contrave combination of naltrexone and bupropion, OHSU has licensed to us, on an exclusive basis, the issued patent underlying the *in vitro* model that we have used for screening combination therapies for impact on neuronal activity. Our rights to this model extend through the expiration of the patent, which is expected to occur in 2024. We have the right to grant sublicenses to third parties for this patented technology, subject to our obligation to pay OHSU a royalty on revenue received by us from the sale of any products covered under such sublicensing arrangements. Under the terms of the agreement, OHSU is solely responsible for the prosecution, maintenance and enforcement (including all costs associated therewith) of this patent; however, we are required to pay 100% of the prosecution and maintenance expenses incurred by OHSU in connection with these patent rights. As of December 31, 2012, we have paid a total of approximately $118,000 in connection with the maintenance and prosecution of this patent. In addition, OHSU has the right to not file any patent application or to abandon any patent or patent application included in the patent rights, in which case it must provide us 60 days' prior written notice and, in response, we may elect at our sole cost to pursue these actions.

Lee Dante License Agreement

In June 2004, we entered into a patent license agreement with Lee G. Dante, M.D., whereby we acquired an exclusive worldwide license to two U.S. patents covering compositions of specified opioid antagonists (including naltrexone) combined with specified antidepressants (including bupropion) and, as such, provide basic composition of matter coverage for the Contrave naltrexone/bupropion combination.

As consideration for this license, we paid upfront fees totaling $100,000 and granted Dr. Dante an option to purchase 73,448 shares of our common stock at an exercise price of $0.10 per share which expires in April 2014. As of December 31, 2010, Dr. Dante has exercised all 73,448 shares of common stock underlying this option grant. We are also obligated to pay a royalty on net sales of products covered by the license. In September 2010, we entered into an amendment to this license agreement with Dr. Dante pursuant to which we agreed to, among other things, provide for a payment to Dr. Dante in the amount of $1 million upon the execution of our collaboration agreement with Takeda, which amount we paid in September 2010. We have the right to grant sublicenses of the patented technology to third parties, subject to our obligation to pay Dr. Dante a royalty on any revenue we receive from such arrangements.

The term of the agreement generally extends until the last licensed patent right expires, which is expected to occur in 2013. Either party may terminate the agreement upon delivery of written notice if the other party commits fraud, willful misconduct, or illegal conduct with respect to the subject matter of the agreement. In addition, either party may terminate the agreement upon delivery of written notice if the other party commits a material breach of its obligations and fails to remedy the breach within a specified period. We may also voluntarily terminate the agreement upon delivery of written notice within a specified time period. In addition, Dr. Dante may terminate the agreement upon specified bankruptcy, liquidation or receivership proceedings.

Under this agreement, we have the responsibility to defend and/or settle any third-party patent infringement claims, assume all costs associated therewith and, to the extent these claims result from our activities or those of our sublicensees and not from Dr. Dante's activities, indemnify him for any damages resulting therefrom. In the case of third-party infringement of the licensed patents, we have the right, but not the obligation, to either settle or prosecute at our own expense any such infringement. Dr. Dante has the right, but not the obligation, to join any suit we commence at our expense and, if we do not undertake action within three months of being made aware of infringing activity, the right to commence his own suit at his expense.

Duke University License Agreement

In March 2004, we entered into a patent license agreement with Duke whereby we acquired an exclusive worldwide license to the Gadde patent. The Gadde patent is a U.S. patent covering the composition of Empatic and methods for using Empatic to treat obesity and reduce the risk of hypertension, diabetes or dyslipidemia. Under the agreement, we also acquired a license to an issued patent covering methods of using zonisamide (including in combination with bupropion) to cause weight loss and an international patent application, and any patents or patent applications that ultimately issue therefrom. The license agreement was amended in December 2004 and July 2006.

As consideration for this license, we issued 442,624 shares of our common stock to Duke and may be required to make future milestone payments totaling $1.7 million upon the achievement of various milestones related to regulatory or commercial events. We are also obligated to pay a royalty on net sales of products covered by the license. We have the right to grant sublicenses to third parties, subject to our obligation to pay Duke a royalty on any revenue we receive from such sublicensing arrangements. In addition, under this agreement we are obligated to pay Duke a specified royalty on sales of products covered by the Weber/Cowley patent applications.

The term of the agreement generally extends until the last licensed patent right expires, which is expected to occur in 2023. Either party may terminate the agreement upon delivery of written notice if the other party commits fraud, willful misconduct, or illegal conduct of the other party with respect to the subject matter of the agreement. In addition, either party may terminate the agreement upon delivery of written notice if the other party commits a material breach of its obligations and fails to remedy the breach within a specified period. We may also voluntarily terminate the agreement upon delivery of written notice within a specified time period. Duke may terminate the agreement upon delivery of written notice if we fail to meet certain specified milestones of the agreement and fail to remedy such a breach within the specified period. In addition, Duke may terminate the agreement upon specified bankruptcy, liquidation or receivership proceedings.

Under this agreement, we have the responsibility to defend and/or settle any third-party patent infringement claims, assume all costs associated therewith and, to the extent these claims result from our activities or those of our sublicensees and not from Duke's activities, indemnify Duke for any damages resulting therefrom. In the case of third-party infringement of the licensed patents, we have the right, but not the obligation, to either settle or prosecute at our own expense any such infringement. Duke has the right, but not the obligation, to join in any suit we commence at our expense and, if we do not undertake action within three months of being made aware of infringing activity, the right to commence its own suit at Duke's expense.

In June 2011, we entered into an amendment to our license agreement. The amendment provides, among other things, for the extension of certain diligence milestones we are required to meet with respect to the development of Empatic. As of December 31, 2012, we have paid to Duke a total of approximately $650,000 to extend such diligence milestones.

GlaxoSmithKline LLC and Glaxo Group Limited License Agreement

In December 2010, we entered into an amended and restated license agreement with GlaxoSmithKline LLC, formerly known as SmithKline Beecham Corporation, and Glaxo Group Limited, or collectively GSK, that amends and restates in its entirety the license agreement we originally entered into with GSK in June 2009. Under the agreement, we obtained a non-exclusive worldwide license from GSK to certain patents covering various formulations of bupropion hydrochloride for use in the development and commercialization of Contrave for the treatment of obesity and disorders of weight management.

The amended and restated agreement primarily clarifies and confirms that certain Canadian patents are part of and included in the patents that were licensed to us from GSK pursuant to the original agreement. Under the amended and restated agreement, GSK retains the responsibility for and control over, at its sole cost and expense, the prosecution and maintenance of the patents licensed to us, other than the Canadian patents, and GSK also has the sole right to, but is not obligated to, bring, at its own expense, an infringement action against any third party in respect of the licensed patents, other than the Canadian patents, and has full control over its conduct, including settlement thereof.

The term of the amended and restated agreement generally extends on a country-by-country basis until the expiration, lapse or invalidation of the last remaining patent or patent application within the licensed patents in such country. We may terminate the agreement with respect to any particular country or in its entirety at any time upon specified written notice to GSK. Either party may terminate the agreement upon delivery of written notice if the other party is in material default or breach of its obligations and fails to remedy the breach within a specified period. In addition, either party may terminate the agreement upon specified bankruptcy, liquidation or receivership proceedings, and the agreement may be terminated by the mutual written agreement of both parties.

Manufacturing

To date, our products used in clinical trials have been produced by outside contractors under our supervision.

We use Patheon Pharmaceuticals and Patheon Inc., or collectively Patheon, to manufacture Contrave and placebo tablets for the Light Study. Patheon currently provides our clinical quantities on a proposal-by-proposal basis under a master agreement for pharmaceutical development services that we originally entered into in February 2007, and amended and restated in March 2010. Either party may terminate the agreement upon notice if the other party commits a material breach of its obligations and fails to remedy the breach within a specified time period. In addition, we may terminate the agreement immediately for any business reason. To date, we have contracted for a sufficient amount of Contrave and placebo tablets to cover the supply needs for the Light Study.

In March 2010, we entered into a manufacturing services agreement with Patheon, pursuant to which Patheon has agreed to manufacture commercial quantities of our Contrave tablet products. Under the terms of the

manufacturing agreement, we are required to purchase a certain percentage of our requirements for our Contrave tablet products intended for commercial sale, provided certain terms and conditions are met.

The initial term of the manufacturing agreement commenced on March 12, 2010 and continues in effect until December 31 st of the year that is five years from the date Contrave first receives approval for marketing from the FDA or any other foreign regulatory agencies competent to grant marketing approvals for pharmaceutical products. Upon expiration of the initial term, the agreement will be automatically renewed for additional two year terms. Patheon may terminate the manufacturing agreement at any time upon specified prior written notice to us. We may also terminate the agreement with specified prior written notice to Patheon, subject to our payment of certain termination amounts. Either party may terminate the agreement effective immediately upon written notice to the other in the event that (1) the other party dissolves, is declared insolvent or bankrupt by a court of competent jurisdiction, (2) a voluntary petition of bankruptcy is filed in any court of competent jurisdiction, or (3) the agreement is assigned for the benefit of creditors. We may terminate the agreement upon specified prior written notice if any governmental or regulatory authority, including, but not limited to, the FDA, takes any action, or raises any objection, that prevents us from importing, exporting, purchasing, or selling our Contrave tablet products. We are also required to give specified advance notice if we intend to no longer order commercial supplies of our Contrave tablet products pursuant to the manufacturing agreement due to the product's discontinuation in the market. Patheon may terminate the agreement upon specified prior written notice to us if we assign any of our rights under the agreement to an assignee that, in the opinion of Patheon acting reasonably, is (1) not a credit worthy substitute for us; or (2) a competitor of Patheon. Moreover, either party may terminate the agreement upon written notice to the other party where the other party has failed to remedy a material breach of any of its representations, warranties, or other obligations under the manufacturing agreement within a specified period of time following receipt of a written notice of the breach, subject to specified terms and conditions.

Patheon has produced and will produce and bottle our Contrave tablet products using naltrexone and bupropion active pharmaceutical ingredient, or API, supplied from various sources, including but not limited to Cilag AG, and Chemi, S.p.A. We have also entered into an agreement with Almac Group for final packaging and distribution of Contrave and placebo bottles for the Light Study.

In January 2009, we entered into a supply agreement with Cilag pursuant to which Cilag will manufacture commercial supplies of naltrexone for use in our drug products. Pursuant to the terms of the supply agreement, we shall pay certain specified prices for such supplies based on the volumes purchased, which prices may be adjusted, subject to specified limitations. In addition, from the period beginning on the first December 31 st following marketing approval by the FDA for our drug product containing naltrexone and continuing through the term of the supply agreement, we are required to purchase from Cilag a specified percentage of our requirements for naltrexone intended for commercial sale in our drug products containing naltrexone, provided that certain terms and conditions are met.

The term of the supply agreement commenced in January 2009 and shall continue in effect until the date that is four years from the period beginning on the first December 31st following marketing approval by the FDA for our drug product containing naltrexone. Either party may terminate the agreement effective immediately upon written notice to the other in the event that (a) the other party dissolves, is declared insolvent or bankrupt by a court of competent jurisdiction, (b) a voluntary or involuntary petition of bankruptcy is filed in any court of competent jurisdiction, or (c) the agreement is assigned for the benefit of creditors. In addition, we may terminate the agreement effective immediately upon written notice in the event that (a) any regulatory agency takes any action, or raises any objection that prevents us from importing, exporting, purchasing or selling naltrexone, (b) our drug product containing naltrexone fails during clinical trials and we withdraw our NDA, (c) we determine, in our sole discretion, to no longer pursue the development and/or commercialization of a drug product containing naltrexone, or (d) a legal proceeding shall be instituted against Cilag, which is reasonably likely to materially adversely affect Cilag's ability to properly perform under the agreement or subject us to any material risk of liability or loss. Moreover, either party may terminate the agreement upon specified written

notice to the other party of a failure by that party to perform or observe any material covenant, condition or agreement to be performed or observed by it under the supply agreement, unless such breach has been cured within the specified notice period.

During any period during the term of the supply agreement in which Cilag for any reason, including, without limitation, a force majeure, fails to deliver the requisite quantities of naltrexone included in any firm commitment purchase order placed by us, within a specified period after the date of delivery confirmed in writing by Cilag or if Cilag otherwise anticipates or notifies us that it will be unable to make delivery of all or a portion of the ordered naltrexone within a specified period after the confirmed date of delivery, then we may refuse such late shipment of naltrexone from Cilag and purchase such quantities under such firm commitment purchase order through a substitute third party supplier. In the event Cilag regains its ability to resume supplying under the supply agreement, our right to purchase naltrexone from the substitute supplier shall terminate.

In December 2009, we entered into a supply agreement with Chemi pursuant to which Chemi will manufacture commercial supplies of bupropion for use in our drug products. Pursuant to the terms of the supply agreement, we shall pay certain specified prices for such supplies based on the volumes purchased, which prices may be adjusted, subject to specified limitations. The supply agreement does not require us to purchase any minimum percentage of our total requirements for bupropion from Chemi.

The initial term of the supply agreement commenced retroactively in November 2009 and shall continue in effect until the date that is four years from the date we first received marketing approval for from the FDA or other governmental agency, or similar regulatory agency or commission in any foreign state or territory for our drug product containing bupropion. This initial term shall be automatically renewed for additional two year terms unless we provide specified written notice of our intent to terminate to Chemi prior to the expiration of the initial term or any extension term, as applicable. Either party may terminate the supply agreement effective immediately upon written notice to the other in the event that (a) the other party dissolves, is declared insolvent or bankrupt by a court of competent jurisdiction, (b) a voluntary or involuntary petition of bankruptcy is filed in any court of competent jurisdiction, (c) the supply agreement is assigned for the benefit of creditors, (d) any regulatory agency takes any action, or raises any objection that prevents us from importing, exporting, purchasing or selling bupropion or our drug product containing bupropion, (e) our drug product containing bupropion fails during clinical trials and we withdraw our NDA, (f) we determine, in our sole discretion, to no longer pursue the development and/or commercialization of our drug product containing bupropion, or (g) a legal proceeding shall be instituted against Chemi, which is reasonably likely to materially adversely affect Chemi's ability to properly perform under the supply agreement or subject us to any material risk of liability or loss. Moreover, either party may terminate the supply agreement upon specified written notice to the other party of a failure by that party to perform or observe any material covenant, condition or agreement to be performed or observed by it under the supply agreement, unless such breach has been cured within the specified notice period.

Other than our supply agreements with Cilag and Chemi, we have no material, long-term commitments or supply agreements with any of our API suppliers. Although we may seek to establish additional long-term supply commitments in the future, we may be required to agree to minimum volume requirements, exclusivity arrangements or other restrictions. We may not be able to enter into additional long-term agreements on commercially reasonable terms, or at all.

In the future, if we are able to achieve approval in the United States or other countries to market and sell our products, we intend to continue to rely on outside contractors for the production of necessary supplies. We do not currently intend to establish our own manufacturing capabilities.

Competition

Treatments for obesity consist of behavioral modification (diet and exercise), pharmaceutical therapies, surgery and device implantation. Modifications to diet and exercise are the preferred initial treatment in obesity.

However, the demands of behavioral modification alone tend to cause significant attrition over time, often resulting in regaining weight. When pharmaceutical therapies are recommended it is generally after behavioral modification alone has failed. Consistent with proposed labeling and as demonstrated in our clinical studies, behavioral modification in combination with Contrave is effective in achieving weight loss.

Orlistat, phentermine/topiramate and lorcaserin are pharmaceutical products that have been approved for the treatment of obesity in the United States. Several older agents, indicated for short-term administration, are amphetamine-like compounds including phentermine, phendimetrazine, benzphetamine and diethylpropion. Of these, phentermine is the most widely used, accounting for approximately 6.2 million prescriptions in the United States in 2009, or approximately $53 million in sales, according to IMS Health. Orlistat is marketed in the United States by Genentech under the brand name Xenical. Orlistat works by inhibiting lipase, an enzyme that aids in the absorption of fat in the gastrointestinal tract. In 2009, orlistat accounted for approximately 151,000 prescriptions in the United States, or approximately $43 million in sales, according to IMS Health. Orlistat was launched in 2007 over-the-counter in the United States at half the prescribed dose by GlaxoSmithKline under the brand name allí. According to GlaxoSmithKline, in 2008, allí accounted for approximately $105 million in sales. In June 2012, Arena obtained FDA approval for its product, locaserin, which it has indicated will be marketed, once launched, in the United States under the name Belviq. In July 2012, Vivus obtained FDA approval for its combination product, phentermine/topiramate. Vivus commercially launched its combination product in the United States under the name Qsymia in September 2012. Vivus, and Arena, if Arena or its partner Eisai Pharmaceuticals, Inc. commercially launches lorcaserin, may build a significant competitive advantage prior to the time we and our collaborative partner are able to market Contrave, or we or any future collaborative partner are able to market Empatic, if approved. If such products are successfully marketed, they could represent additional competition and potential negative pricing pressure with respect to Contrave or Empatic.

In 2012, we conducted physician and patient market research to assess potential growth of the obesity therapeutics market as well as preference shares between Contrave, phentermine/topiramate and lorcaserin. The quantitative market research conducted with 1,000 physicians suggests the market for obesity therapeutics could grow 3 to 4 fold within five years from a 2012 base of approximately 7.8 million prescriptions. The physician research also suggests that Contrave, if approved, would be prescribed at or above the level of each of phentermine/topiramate and locaserin. This was especially true among certain important patient profiles that included some or all of the following characteristics: female; a BMI between 30 and 40; and diabetes. We conducted another market research study that surveyed more than 5,000 patients to assess interest levels between Contrave, phentermine/topiramate and locaserin. The results of this research indicate significant patient interest for Contrave, especially across certain important segments of the obese and overweight patient population, supporting the physician research findings.

Despite the large market opportunity for anti-obesity agents, there are relatively few competitive products in late stage clinical development. Companies pursuing pharmaceutical treatments for obesity include Athersys, Inc., Bristol-Myers Squibb, Neurosearch A/S, Norgine BV, Novo Nordisk A/S, our partner, Takeda, and Zafgen, Inc. Most of these other developmental efforts are directed toward a monotherapeutic approach which we would expect to be subject to the same early plateau of weight loss typically seen. In addition, several agents in a new therapeutic class called cannabanoid antagonists have recently failed or been withdrawn from the market.

There are also surgical approaches to treat severe obesity that are becoming increasingly accepted and could become competitors against our product candidates. Bariatric surgery, including gastric bypass and gastric banding procedures, is employed in more extreme cases, typically for patients with a BMI exceeding 40 or those with a BMI greater than 30 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 patients with a BMI greater than 30 who are experiencing obesity related co-morbidities or patients with a BMI greater than 35 with or without obesity related co-morbidities. Surgery is associated with significant side effects, potential complications and substantial costs and recovery time. Certain device implantations used as therapies, such as neuromodulation,

are not yet approved by the FDA. In addition, other potential approaches which utilize various implantable devices or surgical tools are in development. Some of these approaches are in late stage development and may be approved for marketing. Companies such as Allergan, Inc., Boston Scientific, Covidien Ltd., EnteroMedics, Inc., GI Dynamics, Inc., Johnson & Johnson, and Medtronic, Inc. are all active in the surgical and device space and may have substantially greater resources than we have.

In addition, we may face competition from generic products. Each of bupropion, naltrexone and zonisamide is available in generic form. However, we have undertaken strategies which we believe may impede potential competition from generic products. Supplementing our existing composition patents and patent applications, we have developed formulations and dosages of Contrave and Empatic that we believe may improve patient outcomes and provide further barriers to entry, including intellectual property protection, for potential competitors. We believe there cannot be an AB-equivalence designation for the generic versions of the constituents comprising Contrave and Empatic because of differences in pharmacokinetics between the existing generically available formulations and doses and the formulations and doses we plan to use. For naltrexone and zonisamide, we have selected dosages and are using formulations that are not currently available in generic form and create a different pharmacokinetic profile from the generic forms of these drugs. For bupropion, we are utilizing dosages that are not currently generically available. We believe that our issued, composition and methods-of-use patents will prevent generic firms from manufacturing comparable formulations and from marketing the constituent compounds together. In addition, we believe that practitioners who are seeking to prescribe safe and effective therapy are not likely to prescribe off-label generics in place of Contrave or Empatic because the dosages, pharmacokinetic profile and titration regimens for Contrave and Empatic would not be available using existing generic preparations. Moreover, while general practitioners are the primary prescribers of anti-obesity therapies and are generally familiar with bupropion, they are not the primary prescribers of the other constituents of our product candidates, naltrexone and zonisamide. Accordingly, we believe that general practitioners will be unlikely to prescribe generic compounds with which they are unfamiliar. As a result, we believe that we have established a position with both Contrave and Empatic that will limit generic competition.

Third-Party Reimbursement

Despite the recognition of obesity as a chronic disease and its enormous cost to our health care system, universal coverage of and reimbursement for drugs to treat obesity by both public and private payors is lacking. However, third-party reimbursement for anti-obesity drugs appears to be evolving, including among state Medicaid programs and private commercial plans and pharmacy benefit managers.

Medicaid

The Medicaid program provides health insurance coverage for individuals who are poor and meet certain other eligibility criteria. The program is a federal and state partnership. Within broad federal parameters, each state designs and administers its own program. The federal government shares in the cost of the program by reimbursing states a percentage of their costs.

All states currently provide outpatient prescription drug coverage under their Medicaid programs. States that elect to offer outpatient prescription drug coverage must, with certain exceptions, provide coverage for all FDA-approved drugs of every manufacturer that has entered into a rebate agreement with HHS under the Medicaid Rebate Program.

Medicare

The Medicare program provides health insurance for individuals aged 65 and over and those with serious disability or end-stage renal disease, regardless of income. However, Medicare coverage of obesity treatments is limited. In the fourth quarter of 2011, the Centers for Medicare & Medicaid Services announced that the Medicare program was adding new benefit coverage for prevention with the objective of treating obesity. The new benefit provides for screening for obesity and counseling for eligible beneficiaries by primary care providers

in physician's offices. The benefit includes face to face counseling for up to 12 total months. Current policy authorizes coverage of non-pharmacologic obesity treatments but only when such treatments are an integral and necessary part of a course of treatment for a co-morbid medical condition. Pursuant to this policy, in February 2006, Medicare began covering certain designated bariatric surgical services for Medicare patients with a BMI equal to or greater than 35, who have at least one co-morbidity and have been previously unsuccessful with the medical treatment of obesity. However, the policy reiterates that treatments for obesity alone are not covered because such treatments are not considered reasonable and necessary. In addition, by statute, Medicare's prescription drug benefit does not cover either outpatient prescription weight loss drugs or over-the-counter drugs.

Private Commercial Plans

There is a wide range of coverage by private commercial plans for Xenical. Based on data obtained from Fingertip Formulary databases, almost half of commercial plans reviewed (excluding Blue Cross Blue Shield) listed Xenical on their formularies, typically in a Tier 3 position. In general, plans offer coverage for oral weight loss products only if the benefit is selected by employers. Many plans require prior authorization. Thus, our product candidates for obesity, if approved, may not achieve broad coverage. Moreover, the amount of any coverage provided under the various plans may be minimal. Government policy is a key player in setting trends for coverage of obesity treatments. Private payers may be more likely to add coverage of weight loss products if Medicare provides coverage. We do not expect the success of our obesity product candidates to be entirely contingent on third-party payer coverage and reimbursement, but rather, on acceptance by physicians and people who want to lose weight and are willing to pay for the drugs out of pocket.

Government Regulation

In the United States, prescription drug products are subject to extensive pre- and post-market regulation by the FDA, including regulations that govern the testing, manufacturing, safety, efficacy, labeling, storage, record keeping, advertising and promotion of such products under the Federal Food, Drug, and Cosmetic Act, or FFDCA, and its implementing regulations, and by comparable agencies and laws in foreign countries. Failure to comply with applicable FDA or other requirements may result in civil or criminal penalties, recall or seizure of products, partial or total suspension of production or withdrawal of the product from the market.

FDA approval is required before any new drug, including a new dosage form or use of a previously approved drug, can be marketed in the United States.

New Drug Application (NDA)

An approved NDA by the FDA is generally required before a drug may be marketed in the United States. This process generally involves:

- completion of preclinical laboratory and animal testing in compliance with the FDA's good laboratory practice, or GLP, regulations;
- submission to the FDA of an investigational new drug, or IND, application for human clinical testing which must become effective before human clinical trials may begin;
- performance of adequate and well-controlled human clinical trials to establish the safety and efficacy of the proposed drug product for each intended use;
- satisfactory completion of an FDA pre-approval inspection of the facility or facilities at which the product is produced to assess compliance with the FDA's current Good Manufacturing Practice, or cGMP, regulations; and
- submission to and approval by the FDA of an NDA.

The preclinical and clinical testing and approval process requires substantial time, effort and financial resources, and we cannot be certain that any approvals for our product candidates will be granted on a timely basis, if at all.

Preclinical tests include laboratory evaluation, as well as animal studies to evaluate pharmacology and toxicity. The results of preclinical tests, together with manufacturing information and analytical data, are submitted as part of an IND application to the FDA. The IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA, within the 30-day time period, issues a clinical hold raising concerns or questions about the conduct of the clinical trial, including concerns that human research subjects will be exposed to unreasonable health risks. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before a clinical trial can begin. Submission of an IND may not result in FDA authorization to commence a clinical trial. A separate submission to an existing IND must also be made for each successive clinical trial conducted during product development. Further, an independent institutional review board, or IRB, for each medical center proposing to conduct the clinical trial must review and approve the plan, protocol and informed consent forms for any clinical trial and the IRB must monitor the trial until completed. The FDA, the IRB, or the sponsor may suspend a clinical trial at any time on various grounds, including a finding that the subjects or patients are being exposed to an unacceptable health risk. Clinical testing also must satisfy Good Clinical Practice, or GCP, as set forth in the FDA guidance, and related regulations, including regulations for informed consent.

For purposes of an NDA submission and approval, human clinical trials are typically conducted in the following three or four sequential phases, which may overlap:

- *Phase I:* Studies are initially conducted in a limited population to test the product candidate for safety, dose tolerance, absorption, metabolism, distribution and excretion in healthy humans or, on occasion, in patients, such as cancer patients when the drug is too toxic to be ethically given to healthy individuals.
- *Phase II:* Studies are generally conducted in a limited patient population to identify possible adverse effects and safety risks, to determine the efficacy of the product for specific targeted indications and to determine dose tolerance and optimal dosage. Multiple Phase II clinical trials may be conducted by the sponsor to obtain information prior to beginning larger and more expensive Phase III clinical trials.
- *Phase III:* These are commonly referred to as pivotal studies. When Phase II evaluations demonstrate that a dose range of the product is effective and has an acceptable safety profile, Phase III clinical trials are undertaken in large patient populations to further evaluate dosage, to provide substantial evidence of clinical efficacy and to further test for safety in an expanded and diverse patient population at multiple, geographically-dispersed clinical trial sites.
- *Phase IV:* In some cases, FDA may condition approval of an NDA for a product candidate on the sponsor's agreement to conduct additional clinical trials after NDA approval. In other cases, a sponsor may voluntarily conduct additional clinical trials post approval to gain more information about the drug. Such post approval trials are typically referred to as Phase IV studies.

Because our product candidates are fixed-dose combination prescription drugs, we will need to comply with the FDA's regulation that requires that we show that each component of each product contributes to the claimed effects. This means that our clinical trials for our product candidates will need to evaluate the combination as compared to each component separately as well as to placebo. In addition, in designing our clinical trials, we will also need to consider the draft guidance for developing products for weight management issued by the FDA in February 2007, which includes recommendations on the design of clinical trials evaluating the efficacy and safety of products intended to treat obesity, and any guidance provided by the FDA following the general obesity advisory committee meeting that FDA convened in late March 2012 to discuss cardiovascular safety assessment of obesity drugs. The results of product development, preclinical studies and clinical trials are submitted to the FDA as part of an NDA. NDAs must also contain extensive manufacturing information.

After completion of the required clinical testing, an NDA is prepared and submitted to the FDA. FDA approval of the NDA is required before marketing of the product may begin in the United States. The cost of preparing and submitting an NDA is substantial. The Prescription Drug User Fee Act, which has been reauthorized four times by Congress, requires the payment of user fees with the submission of NDAs, including 505(b)(2) NDAs. These application fees are substantial ($1,958,800 in the FDA's Fiscal Year 2013) and will likely increase in future years. The FFDCA provides for waiver of the application fee for the first NDA for a small business under certain circumstances. In February 2010, we were granted a waiver of this application fee for our Contrave NDA. This one time waiver will not be available to us upon submission of NDAs, if any, for our other product candidates in the future. Manufacturers and sponsors of approved drugs are subject to annual product and establishment fees of $526,500 per manufacturing establishment and $98,380 per product. The FDA has agreed to certain performance goals in the review of NDAs. Most applications for non-priority drug products have been reviewed within ten months while most applications for priority review drugs, that is, drugs that the FDA determines represent a significant improvement over existing therapy, are reviewed in six months. Based on FDA announcements about changing PDUFA goals, it is likely that the NDA, if any, for Empatic will be reviewed on a twelve-month cycle by the FDA, as opposed to the shorter eight-month cycle projected to be given to priority review drugs after 2012. The review process is often extended by the submission of additional information or clarification during the review. The FDA may refer the application to an advisory committee for review, evaluation and recommendation as to whether the application should be approved. The FDA is not bound by the recommendation of an advisory committee, but it generally follows such recommendations.

Before approving an NDA, the FDA will typically inspect one or more clinical trial sites to assure compliance with GCP. Additionally, the FDA will inspect the facility or the facilities at which the drug is manufactured. The FDA will not approve the product unless compliance with cGMP and GCP is satisfactory and the NDA contains data that provide substantial evidence that the drug is safe and effective in the indication studied. The FDA may deny approval of an NDA if the applicable regulatory criteria are not satisfied, or it may require additional data including additional pivotal Phase III clinical trials. Even if such data are submitted, the FDA may ultimately decide that the NDA does not satisfy the criteria for approval. Data from clinical trials are not always conclusive and FDA may interpret data differently than we do.

Upon completion of its review of the NDA, FDA issues an approval letter or a complete response letter. A complete response letter generally outlines the deficiencies in the submission and may require substantial additional testing or information in order for the FDA to reconsider the application. If and when those deficiencies have been addressed to the FDA's satisfaction in a resubmission of the NDA, the FDA will issue an approval letter. The FDA's goal is to review such resubmissions in 2 or 6 months depending on the type of information included.

An approval letter authorizes commercial marketing of the drug with specific prescribing information for specific indications. As a condition of NDA approval, the FDA may require substantial post-approval testing and surveillance to monitor the drug's safety or efficacy and may impose other conditions, including labeling restrictions which can materially affect the potential market and profitability of the drug. Once granted, product approvals may be withdrawn if compliance with regulatory standards is not maintained or problems are identified following initial marketing.

Special Protocol Assessment

An SPA is a written agreement with the FDA on the details of the design and planned analysis for a clinical trial. It is intended to form the basis for an NDA and may only be changed through a written agreement between the sponsor and the FDA. An SPA is generally binding upon the FDA unless the FDA determines that there are public health concerns unrecognized at the time the SPA agreement was entered into, other new scientific concerns regarding product safety or efficacy arise, or if the sponsor fails to comply with the agreed upon trial protocols.

The Hatch-Waxman Act

In 1984, Congress enacted the Drug Price Competition and Patent Term Restoration Act of 1984, also known as the Hatch-Waxman Act. In seeking approval for a drug through an NDA, applicants are required to list with the FDA each patent with claims that cover the applicant's product. Upon approval of a drug, each of the patents listed in the application for the drug is then published in the FDA's Approved Drug Products with Therapeutic Equivalence Evaluations, commonly known as the Orange Book. Drugs listed in the Orange Book can, in turn, be cited by potential competitors in support of approval of an abbreviated new drug application, or ANDA. An ANDA provides for marketing of a drug product that has the same active ingredients in the same strengths and dosage form as the listed drug and has been shown through bioequivalence testing to be therapeutically equivalent to the listed drug. ANDA applicants are not required to conduct or submit results of pre-clinical or clinical tests to prove the safety or effectiveness of their drug product, other than the requirement for bioequivalence testing. Drugs approved in this way are commonly referred to as "generic equivalents" to the listed drug, and can often be substituted by pharmacists under prescriptions written for the original listed drug.

The ANDA applicant is required to certify to the FDA concerning any patents listed for the approved product in the Orange Book. Specifically, the applicant must certify that: (i) the required patent information has not been filed; (ii) the listed patent has expired; (iii) the listed patent has not expired, but will expire on a particular date and approval is sought after patent expiration; or (iv) the listed patent is invalid or will not be infringed by the new product. A certification that the new product will not infringe the already approved product's listed patents or that such patents are invalid is called a Paragraph IV certification. If the applicant does not challenge the listed patents, the ANDA application will not be approved until all the listed patents claiming the referenced product have expired.

If the ANDA applicant has provided a Paragraph IV certification to the FDA, the applicant must also send notice of the Paragraph IV certification to the NDA and patent holders once the ANDA has been accepted for filing by the FDA. The NDA and patent holders may then initiate a patent infringement lawsuit in response to the notice of the Paragraph IV certification. The filing of a patent infringement lawsuit within 45 days of the receipt of a Paragraph IV certification automatically prevents the FDA from approving the ANDA until the earlier of 30 months, expiration of the patent, settlement of the lawsuit or a decision in the infringement case that is favorable to the ANDA applicant.

The ANDA application also will not be approved until any non-patent exclusivity, such as exclusivity for obtaining approval of a new chemical entity, listed in the Orange Book for the referenced product has expired. Federal law provides a period of five years following approval of a drug containing no previously approved active ingredients, during which ANDAs for generic versions of those drugs cannot be submitted unless the submission contains a Paragraph IV challenge to a listed patent, in which case the submission may be made four years following the original product approval. Federal law provides for a period of three years of exclusivity following approval of a listed drug that contains previously approved active ingredients but is approved in a new dosage form, route of administration or combination, or for a new use, the approval of which was required to be supported by new clinical trials conducted by or for the sponsor, during which the FDA cannot grant effective approval of an ANDA based on that listed drug.

Section 505(b)(2) New Drug Applications

As an alternate path to FDA approval for modifications to products previously approved by the FDA, an applicant may file an NDA under Section 505(b)(2) of the FFDCA. Section 505(b)(2) was enacted as part of the Hatch-Waxman Act. This statutory provision permits the filing of an NDA where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference. The Hatch-Waxman Act permits the applicant to rely upon the FDA's findings of safety and effectiveness for previously approved products. The FDA may then approve the new product candidate for all or some of the label indications for which the referenced product has been approved, as well as for any new indication for which the Section 505(b)(2) applicant has submitted its own data.

The FDA requires companies to perform additional studies or measurements to support the change from the approved product. We submitted our initial NDA for Contrave and intend to submit our initial NDA for Empatic under Section 505(b)(2), based on the extensive safety information that has been collected for the approved drug products that are incorporated in these product candidates. To the extent that a Section 505(b)(2) application relies on the FDA's finding of safety and effectiveness of a previously-approved drug, the applicant is required to certify to the FDA concerning any patents listed for the approved product in the FDA's publication called "Approved Drug Products with Therapeutic Equivalence Evaluations," otherwise known as the "Orange Book." Specifically, the applicant must certify when the application is submitted that: (1) there is no patent information listed; (2) the listed patent has expired; (3) the listed patent has not expired, but will expire on a particular date and approval is sought after patent expiration; or (4) the listed patent is invalid or will not be infringed by the manufacture, use or sale of the product. A certification that the new product will not infringe the already approved product's Orange Book listed patents or that such patents are invalid is called a paragraph IV certification. If the applicant has provided a paragraph IV certification to the FDA, the applicant must also send notice of the paragraph IV certification to the patent holder and the NDA holder. When we submitted our NDA for Contrave, we made paragraph IV certifications that Contrave does not infringe the bupropion patents listed in the Orange Book and sent the appropriate notice to the patent holder and NDA holder once we received confirmation from the FDA that our NDA was sufficiently complete to permit a substantive review. We intend to do the same if and when we submit our NDA for Empatic. In the event that the patent holder or NDA holder files a patent infringement lawsuit against us within 45 days of its receipt of our paragraph IV notification, such lawsuit would automatically prevent the FDA from approving our Section 505(b)(2) NDA until the earliest of 30 months, expiration of the patent (2013), settlement of the lawsuit or a decision in the infringement case that is favorable to us. Any such patent infringement lawsuit could be costly, take a substantial amount of time to resolve and divert management resources.

If we obtain FDA approval for either Contrave or Empatic, we could obtain three years of Hatch-Waxman marketing exclusivity for such product, assuming we conduct or sponsor a new clinical investigation that is essential to approval of our NDA. Under this form of exclusivity, the FDA would be precluded from approving a generic drug application or, in some cases, another 505(b)(2) application for a drug product for the protected conditions of approval (for example, a product that incorporates the change or innovation represented by our product) for a period of three years, although the FDA may accept and commence review of such applications. However, this form of exclusivity would not prevent the FDA from approving an NDA that relies on its own clinical data to support the change or innovation. Further, if another company obtains approval for either product candidate for the same indication we are studying before we do, our approval could be blocked until the other company's Hatch-Waxman marketing exclusivity expires.

Pediatric Information

Under the Pediatric Research Equity Act of 2003, or PREA, NDAs or supplements to NDAs must contain data to assess the safety and effectiveness 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 drug is safe and effective. The FDA may grant deferrals for submission of data or full or partial waivers. Unless otherwise required by regulation, PREA does not apply to any drug for an indication for which orphan designation has been granted. The Best Pharmaceuticals For Children Act, or BPCA, provides sponsors with an additional 6-month period of market exclusivity on all forms of the drug containing the active moiety, if the sponsor submits results of pediatric studies specifically requested by FDA under BPCA. In order to receive the BPCA exclusivity, the drug must have other existing patent or exclusivity protection in effect.

Post-Approval Requirements

Once an NDA is approved, a product will be subject to certain post-approval requirements. We and our contract manufacturers are required to comply with applicable FDA manufacturing requirements contained in the FDA's cGMP regulations. cGMP regulations require, among other things, quality control, and quality assurance

as well as the corresponding maintenance of records and documentation. The manufacturing facilities for our products must meet cGMP requirements to the satisfaction of the FDA pursuant to a pre-approval inspection before we can use them to manufacture our products for commercial distribution. We and our third-party manufacturers are also subject to periodic inspections of facilities by the FDA and other authorities, including procedures and operations used in the testing and manufacture of our products to assess our compliance with applicable regulations.

Adverse experiences associated with the use of the drug must be reported to the FDA and could result in the imposition of market restrictions through labeling changes or in product removal. Product approvals may be withdrawn if compliance with regulatory requirements is not maintained or if problems concerning safety or efficacy of the product occur following approval.

Failure to comply with statutory and regulatory requirements subjects a manufacturer to possible legal or regulatory action, including Warning Letters, the seizure or recall of products, injunctions, consent decrees placing significant restrictions on or suspending manufacturing operations, and civil and criminal penalties.

The FDA can require post-approval studies and clinical trials if the FDA finds, after approving the drug, that scientific data, including information regarding related drugs, render it appropriate. The purpose of such studies would be to assess a known serious risk or signals of serious risk related to the drug or to identify an unexpected serious risk when available data indicates the potential for a serious risk. The FDA may also require a labeling change if it becomes aware of new safety information that it believes should be included in the labeling of a drug.

With respect to post-market product advertising and promotion, the FDA prohibits, restricts or otherwise imposes regulatory requirements on certain activities, including direct-to-consumer advertising, off-label promotion, industry-sponsored scientific and educational activities, and promotional activities involving the internet. The FDA has very broad enforcement authority under the FFDCA, and failure to abide by these regulations can result in penalties, including the issuance of a Warning Letter directing entities to correct deviations from FDA standards, a requirement that future advertising and promotional materials be pre-cleared by the FDA, and federal civil and criminal investigations and prosecutions. State enforcement actions relating to promotional violations are also becoming more common.

Other Regulatory Requirements

The FDA can require a drug-specific REMS to ensure the benefits of the drug outweighs the risks. In determining whether a REMS is necessary, the FDA must consider the size of the population likely to use the drug, the seriousness of the disease or condition to be treated, the expected benefit of the drug, the duration of treatment, the seriousness of known or potential adverse events and whether the drug is a new molecular entity. If the FDA determines a REMS is necessary, a sponsor must submit a proposed REMS as part of its application, or if the request is made post-approval, not later than 120 days after the FDA notifies the drug sponsor. A REMS may be required to include various elements, such as a medication guide or patient package insert, a communication plan to educate health care providers of the drug's risks, limitations on how a drug may be prescribed or dispensed or other measures that the FDA deems necessary to assure the safe use of the drug. REMS programs must be evaluated on an ongoing basis and the FDA may require changes needed to address ongoing safety issues or corrective actions to address any noncompliance.

We are also subject to various laws and regulations regarding laboratory practices, the experimental use of animals, and the use and disposal of hazardous or potentially hazardous substances in connection with our research. In each of these areas, as above, the federal government has broad regulatory and enforcement powers, including the ability to levy fines and civil penalties, suspend or delay issuance of approvals, seize or recall products, and withdraw approvals, any one or more of which could have a material adverse effect on us.

In addition to FDA restrictions on marketing of pharmaceutical products, several other types of state and federal laws have been applied to restrict certain marketing practices in the pharmaceutical industry in recent

years. These laws include anti-kickback statutes and false claims statutes. The federal healthcare program anti-kickback statute prohibits, among other things, knowingly and willfully offering, paying, soliciting or receiving remuneration to induce or in return for purchasing, leasing, ordering or arranging for the purchase, lease or order of any healthcare item or service reimbursable under Medicare, Medicaid or other federally financed healthcare programs. This statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on the one hand and prescribers, purchasers and formulary managers on the other. Violations of the anti-kickback statute are punishable by imprisonment, criminal fines, civil monetary penalties and exclusion from participation in federal healthcare programs. Although there are a number of statutory exemptions and regulatory safe harbors protecting certain common activities from prosecution or other regulatory sanctions, the exemptions and safe harbors are drawn narrowly, and practices that involve remuneration intended to induce prescribing, purchases or recommendations may be subject to scrutiny if they do not qualify for an exemption or safe harbor.

Federal false claims laws prohibit any person from knowingly presenting, or causing to be presented, a false claim for payment to the federal government, or knowingly making, or causing to be made, a false statement to have a false claim paid. Recently, several pharmaceutical and other healthcare companies have been prosecuted under these laws for allegedly inflating drug prices they report to pricing services, which in turn were used by the government to set Medicare and Medicaid reimbursement rates, and for allegedly providing free product to customers with the expectation that the customers would bill federal programs for the product. In addition, certain marketing practices, including off-label promotion, may also violate false claims laws. The majority of states also have statutes or regulations similar to the federal anti-kickback statute and false claims laws, which apply to items and services reimbursed under Medicaid and other state programs, or, in several states, apply regardless of the payor.

In addition, the Patient Protection and Affordable Care Act, or PPACA, and several states have enacted laws affecting pharmaceutical marketing and advertising practices, including laws affecting interactions with health care professionals. States may require, and PPACA will require, pharmaceutical manufacturers to report their sales and marketing expenses, which may include payments to health care professionals. States may also require compliance with a marketing code of conduct and require certification of compliance with such code be submitted to a state agency or a posted on the pharmaceutical company's website. Companies must also be registered or licensed by the federal and state governments prior to manufacturing or distributing prescription drug products.

Outside the United States, our ability to market a product is contingent upon receiving marketing authorization from the appropriate regulatory authorities. The requirements governing marketing authorization, pricing and reimbursement vary widely from country to country. At present, foreign marketing authorizations are applied for at a national level, although within the European Union registration procedures are available to companies wishing to market a product in more than one European Union member state. The regulatory authority generally will grant marketing authorization if it is satisfied that we have presented it with adequate evidence of safety, quality and efficacy.

DEA Regulation

Naltrexone, one of the components of Contrave, is manufactured from semi-synthetic opiates. Although naltrexone is not a narcotic or a controlled substance, manufacturing of naltrexone API is subject to regulation by the U.S. Drug Enforcement Administration, or DEA, because the starting material is regulated. Controlled substances are those drugs that appear on one of five schedules promulgated and administered by the DEA under the Controlled Substances Act, or CSA. The CSA governs, among other things, the distribution, recordkeeping, handling, security, and disposal of controlled substances. Our third-party suppliers of naltrexone must be registered by the DEA in order to engage in these activities, and are subject to periodic and ongoing inspections by the DEA and similar state drug enforcement authorities to assess ongoing compliance with the DEA's regulations. The manufacturers must also obtain an annual quota from the DEA to obtain sufficient material to manufacture substances derived from opiates. Any failure to comply with these regulations could lead to a

variety of sanctions, including the revocation, or a denial of renewal, of DEA registration, injunctions, or civil or criminal penalties. The failure to obtain adequate quota can also limit the manufacturing capacity of the manufacturer.

European Union Drug Review and Approval

In the EEA (which is comprised of the 27 Member States of the European Union plus Norway, Iceland and Liechtenstein), medicinal products can only be commercialized after obtaining a Marketing Authorization, or MA. There are two types of MA:

The Community MA, which is issued by the European Commission through the Centralized Procedure, based on the opinion of the 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 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.

Contrave is eligible for the Centralized Procedure. We have initiated activities with the EMA to enable the submission of a Community MA application supporting potential approval of Contrave under the centralized procedure. After submission and validation of a Community MA application, the EMA's CHMP generally has 210 days to complete its assessment and adopt an opinion on whether or not to recommend the granting of the Community MA. The 210 days period does not include the anticipated "clock stops" at specified points in the procedure, typically at day 120 (Consolidated List of Questions) and at day 180 (List of Outstanding Issues). The clock stops allow time for us to address the outstanding questions or issues raised by the CHMP. At day 180, depending on the List of Outstanding Issues, an oral hearing with the CHMP may be required to address specific issues. Assuming a positive opinion from the CHMP, final marketing authorization is generally granted by the European Commission on day 277 of the procedure, not counting clock stops as noted above. We expect to submit a Contrave marketing authorization around the time of the resubmission of the Contrave NDA. As a result, we are also in the process of establishing an agreed-to pediatric investigation plan, or PIP, with the EMA's Pediatric Committee. An agreed PIP is required before submitting the Community MA application.

Employees

As of March 13, 2013, we had 41 full-time employees and two part-time employees, consisting of clinical development, medical affairs, regulatory affairs, marketing, technical operations and administration. We consider our relations with our employees to be good.

Research and Development

Our research and development expenses totaled $73.9 million, $12.8 million and $28.1 million in the years ended December 31, 2012, 2011 and 2010, respectively.

About Orexigen

We were incorporated in Delaware in September 2002. Our principal offices are located at 3344 N. Torrey Pines Court, Suite 200, La Jolla, California 92037, and our telephone number is (858) 875-8600. Our website address is www.orexigen.com. Information found on, or accessible through, our website is not a part of, and is not incorporated into, this Annual Report on Form 10-K.

Available Information

We file electronically with the U.S. Securities and Exchange Commission our Annual Report on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and amendments to reports filed pursuant to Section 13(a) and 15(d) of the Securities Exchange Act of 1934, as amended. We make available on our website at www.orexigen.com, free of charge, copies of these reports, as soon as reasonably practicable after we electronically file such material with, or furnish it to, the SEC. Copies of our annual report will also be made available, free of charge, upon written request.

The public may read and copy any materials filed by us with the SEC at the SEC's Public Reference Room at 100 F Street, NE, Washington, DC 20549. The public may obtain information on the operation of the Public Reference Room by calling the SEC at 1-800-SEC-0330. The SEC maintains an Internet site that contains reports, proxy and information statements and other information regarding issuers that file electronically with the SEC at http://www.sec.gov. The contents of these websites are not incorporated into this filing. Further, our references to the URLs for these websites are intended to be inactive textual references only.

Item 1A. Risk Factors.

You should carefully consider the following risk factors, as well as the other information in this report, before deciding whether to purchase, hold or sell shares of our common stock. The occurrence of any of the following risks could harm our business, financial condition, results of operations and/or growth prospects or cause our actual results to differ materially from those contained in forward-looking statements we have made in this report and those we may make from time to time. You should consider all of the factors described when evaluating our business.

Risks Related to Our Business and Industry

Our success depends substantially on our product candidates, Contrave ® (naltrexone/bupropion, each in a sustained release, or SR, formulation) and Empatic™ (zonisamide/bupropion, each in a SR formulation). We cannot be certain that either product candidate will receive regulatory approval or be successfully commercialized.

We currently have only a limited number of product candidates in development, and our business currently depends entirely on their successful development and commercialization. We currently have no drug products approved for sale, and we may never be able to develop marketable drug products. The research, testing, manufacturing, labeling, approval, sale, marketing and distribution of drug products are subject to extensive regulation by the U.S. Food and Drug Administration, or FDA, and other regulatory authorities in the United States and other countries, whose regulations differ from country to country. Neither we nor our collaborative partner for Contrave in North America, Takeda Pharmaceutical Company Limited, or Takeda, are permitted to market our product candidates in the United States until we receive approval of a New Drug Application, or NDA, from the FDA, or in any foreign countries until we receive the requisite approval from the regulatory authorities of such countries.

In January 2011, we received a complete response letter, or CRL, from the FDA regarding our NDA for Contrave. The CRL indicated that the FDA could not approve the NDA in its present form primarily due to concerns regarding the cardiovascular safety profile of Contrave when used long-term in a population of overweight and obese subjects. The CRL stated that before our NDA could be approved, we must conduct a randomized, double-blind, placebo-controlled trial of sufficient size and duration to demonstrate that the risk of major adverse cardiovascular events, or MACE, in overweight and obese patients treated with Contrave does not adversely affect the drug's benefit-risk profile. Our near-term success is substantially dependent on the approval of the Contrave NDA.

In September 2011, following a meeting with senior officials in the FDA's Office of New Drugs, or OND, we received written correspondence from the director of the OND detailing the OND's design requirements for a randomized, double-blind, placebo-controlled cardiovascular outcomes trial, or CVOT, for Contrave that would address the CRL. The CVOT will evaluate the occurrence of MACE in patients participating in the study. Importantly, if the interim analysis excludes a doubling of risk of MACE in patients receiving Contrave compared to placebo, we plan to resubmit the Contrave NDA to the FDA for approval. The exclusion of a doubling of risk of MACE was established as the threshold for approvability of Contrave during discussions with the FDA prior to the start of the CVOT. An interim analysis is planned once the CVOT's independent Data Monitoring Committee has determined that sufficient information has been gathered for the analysis that would include at least 87 adjudicated MACE. In February 2012 we reached agreement with the FDA on a Special Protocol Assessment, or SPA, for the CVOT. A SPA is a written agreement with the FDA on the details of the design and planned analysis for a clinical trial. A SPA is generally binding upon the FDA unless a substantial scientific issue essential to determining safety or efficacy is identified after the trial begins. Although we are not aware of any such issue, there is no assurance that the FDA will ultimately consider our SPA to be binding. Moreover, any change to the CVOT protocol can invalidate the SPA. If the FDA does not consider the SPA to be binding, the agency could assert that additional trial or data are required to support a regulatory submission.

In October 2012, we received a response to a formal dispute resolution request from the FDA's Center for Drug Evaluation and Research, or CDER. We had requested that Contrave be considered for approval on the basis of existing data together with a postmarketing requirement to supply the interim analysis of the CVOT shortly after approval. CDER denied this request, reaffirming that the cardiovascular outcomes data from the interim analysis of the CVOT is required prior to approval; however, CDER indicated that it was highly supportive of the exploration of a faster path to resubmission of the Contrave NDA. In January 2013, the FDA's Division of Metabolism and Endocrinology Products, or DMEP, proposed a resubmission procedure that would allow the independent Data Monitoring Committee's summary report of the CVOT interim analysis to form the basis of the resubmission of the Contrave NDA. The complete clinical study report for the interim analysis, which would ordinarily form the basis for the NDA resubmission filing, would be provided to the FDA during its review of the NDA within 60 days of the NDA resubmission.

We initiated the CVOT, which we refer to as the Light Study, in June 2012, and completed screening in December 2012 which resulted in approximately 8,900 patients randomized to treatment. We enrolled a patient population that we predicted would have an annualized MACE rate between 1% and 2%. The timing of the interim analysis and the Contrave NDA resubmission is dependent on the timing of MACE observed in the Light Study. The observed MACE rate may differ materially from the modeled MACE rate due to a number of factors, including but not limited to, short observation times, non-linear rates of occurrence of MACE, patients lost to follow-up and low predictive power of the modeling. We are preparing to be ready to conduct the interim analysis and resubmit the Contrave NDA in 2013. However, if the observed MACE rate is at or near the low end of the targeted range of 1% to 2%, the resubmission of the Contrave NDA may not occur until early 2014.

Conducting the Light Study in accordance with the SPA and performing any additional development activities that the FDA may require in connection with the Contrave NDA will be a lengthy, expensive, complex and uncertain process that will require the expenditure of substantial resources. We can provide no assurance that the results of the Light Study would support approval of the NDA. In addition, we cannot provide assurance that we will be able to conduct the activities, including the Light Study, necessary to re-submit our NDA for Contrave or that the FDA will approve such resubmission as a result of the factors identified. If we do address the issues identified in the CRL, we will need to resubmit the NDA to the FDA, which would typically result in an additional six month review cycle by the FDA.

The FDA has substantial discretion in the drug approval process, including the ability to delay, limit or deny approval of a product candidate for many reasons. For example:

- the FDA may not deem a product candidate safe and effective;
- the FDA may not find the data from preclinical studies and clinical trials, including the Light Study, sufficient to support approval;
- the FDA may not agree with our interpretation and characterization of efficacy and safety data from our clinical trials, including the Light Study;
- the FDA may require additional preclinical or clinical studies;
- the FDA may not approve of our third-party manufacturers' processes and facilities;
- the FDA may not approve of the formulation and/or the specifications of a product candidate;
- the FDA may not agree with our proposed labeling; or
- the FDA may change its approval policies, adopt new regulations or provide new guidance.

In addition, the FDA issued draft guidance on developing products for weight management in February 2007. The draft guidance provides recommendations on the design of studies evaluating the efficacy and safety of products intended to treat obesity. It also provides guidance on the general efficacy benchmarks required in pivotal trials for comparison against placebo. The FDA is not required to follow the draft guidance and can

change this guidance, which could require us to conduct additional clinical trials for Contrave (in addition to the Light Study), or create other requirements that could have the effect of preventing or delaying approval. For example, the FDA held an advisory committee in late March 2012 to discuss cardiovascular safety assessment of obesity drugs. In that meeting, the Endrocrinologic and Metabolic Drugs Advisory Committee, or EMDAC, voted 17 to 6 that obesity drugs without a theoretic risk or signal for cardiovascular harm should be required to rule out a certain degree of excess cardiovascular risk with a cardiovascular outcomes trial or any appropriately sized meta-analysis of Phase II and Phase III MACE data. Although we received written assurance from the OND that such advisory committee would not impact the CVOT advice provided in their letter, we cannot be assured of the outcome of that meeting or its effect on the SPA, draft guidance or on the development and approvability of our obesity product candidates. For example, we can provide no assurance that DMEP's interpretation of the input received from the March 2012 EMDAC meeting will not result in changes to the issued guidance regarding the development of obesity compounds, the Light Study design, or the need to conduct additional trials prior to re-submitting the Contrave NDA.

Our other product candidate, Empatic, has been evaluated in Phase II clinical trials and it will need to successfully complete two or more pivotal trials, as well as potential additional non-pivotal clinical trials we may be required to conduct based on feedback we may receive from the FDA. Similar to Contrave, obtaining approval of an NDA for Empatic will be a lengthy, expensive, complex and uncertain process that will require the expenditure of substantial resources. In addition, Empatic contains bupropion, the same active ingredient that gave rise to the FDA's concerns regarding the cardiovascular safety profile of Contrave, which depending on the result of the NDA for Contrave and any additional studies we conduct for it, may adversely affect the development and regulatory approval prospects of Empatic.

In our recent series of discussions with the FDA on the continued development of Empatic, the FDA stated that Phase III data for Empatic may be sufficient to support submission of an NDA without data from a cardiovascular outcomes trial. The FDA indicated that as long as the placebo-subtracted changes in body weight, blood pressure and heart rate for Empatic are similar to or more favorable than the placebo-subtracted changes observed with Contrave, and there are no signals of cardiovascular concern in the Empatic development program, reassuring results of a cardiovascular outcomes trial with Contrave will be sufficient. In addition, while the FDA reiterated its belief that the preclinical teratogenicity data for zonisamide and the pregnancy outcome data with Empatic from the Phase II clinical trials are very concerning, it will allow Phase III studies of Empatic to include women of childbearing potential with a body mass index, or BMI, >27kg/m^2 in the presence of at least one weight-related comorbidity such as hypertension, type 2 diabetes mellitus or dyslipidemia and a BMI >30 kg/m^2 without additional restrictions if appropriate safety measures and adequate informed consent are provided. However, we can provide no assurance that such guidance by the FDA related to Empatic will not change prior to or during any continued development of Empatic. The FDA noted that similar safety measures and understanding of risk in the Phase III trials may need to be applied in the intended marketed population if Empatic is approved. The FDA added that additional worrisome pregnancy outcome data in the Empatic trials may have an impact on approvability, labeling or risk evaluation and mitigation strategy, or REMS.

Even if we eventually receive approval of an NDA for Contrave, the FDA may grant approval contingent on the performance of costly additional clinical trials which may be required after approval. The FDA also may approve Contrave for fewer or more limited indications or a narrower patient population than we originally requested, and the FDA may not approve the labeling that we and our collaborative partner believe is necessary or desirable for the successful commercialization of Contrave. Any failure to obtain regulatory approval of Contrave would limit our ability to ever generate revenues (and any failure to obtain such approval for all of the indications and labeling claims we deem desirable could reduce our potential revenue), would potentially harm the development prospects of Empatic and would have a material and adverse impact on our business.

Our SPA with the FDA relating to the Contrave CVOT does not guarantee any particular outcome from regulatory review of the trial or the product candidate, including NDA approval.

The protocol for the Light Study was reviewed by the FDA under its SPA process, which allows for FDA evaluation of a clinical trial protocol in support of an NDA, and provides an agreement that the study design, including trial size, clinical endpoints and/or data analyses are acceptable to the FDA. However, the SPA agreement is not a guarantee of approval, the FDA retains the right to require additional testing and we cannot be certain that the design of, or data collected from, the Light Study will be adequate to demonstrate the safety of Contrave, or otherwise be sufficient to support FDA or any foreign regulatory approval. Although the SPA agreement calls for review of interim data at certain times prior to completion, there is no assurance that any such review will result in early approval. Further, the SPA agreement is not binding on the FDA if public health concerns unrecognized at the time the SPA agreement was entered into become evident, other new scientific concerns regarding product safety or efficacy arise, or if we fail to comply with the agreed upon trial protocols. The March 2012 EMDAC meeting, as well as the FDA's interpretation of the input received at the meeting, heightens these risks. While the FDA stated that the March 2012 EMDAC meeting will not impact the advice provided in the OND's letter and the agency will honor the advice provided, we cannot be certain that the FDA will not seek to alter the agreement reached in the SPA. In addition, the SPA agreement may be changed by us or the FDA on written agreement of both parties, and the FDA retains significant latitude and discretion in interpreting the terms of the SPA agreement and the data and results from the Light Study. As a result, we do not know how the FDA will interpret the parties' respective commitments under the SPA agreement, how it will interpret the data and results from the Light Study, or whether Contrave will receive any regulatory approvals as a result of the SPA agreement or the Light Study. Therefore, significant uncertainty remains regarding the clinical development and regulatory approval process for Contrave.

Our clinical trials, including the Light Study, may fail to demonstrate acceptable levels of safety or efficacy of our product candidates, which could prevent or significantly delay their regulatory approval.

Our product candidates are prone to the risks of failure inherent in drug development. Before obtaining regulatory approvals for the commercial sale of Contrave, Empatic or any other product candidate for a target indication, we must demonstrate with substantial evidence gathered in adequate and well-controlled clinical trials, and, with respect to approval in the United States, to the satisfaction of the FDA and, with respect to approval in other countries, similar regulatory authorities in those countries, that the product candidate is safe and effective for use for that target indication. Based on our communications with the FDA, we must conduct a cardiovascular outcomes trial to assess Contrave compared to placebo on the occurrence of MACE, including nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death in overweight and obese patients. The FDA has indicated that Contrave could be approved prior to completion of the cardiovascular outcomes trial based on the resubmission of interim data. We and the FDA estimate that such a study would require approximately 87 total MACE events by the interim data analysis to enable resubmission of the Contrave NDA for approval. In February 2012 we reached agreement with the FDA on the SPA for the CVOT. We initiated the CVOT, which we refer to as the Light Study, in June 2012. We can provide no assurance that the Light Study will demonstrate acceptable levels of cardiovascular risk or that the results of the Light Study will support approval of the Contrave NDA. Although we received written assurance from the OND that the March 2012 EMDAC meeting would not impact the advice provided in their letter, we cannot assure you that the DMEP's interpretation of the input received from the March 2012 EMDAC meeting would not result in changes to the Light Study design, issued guidance regarding the development of obesity compounds or the need to conduct additional trials prior to re-submitting the Contrave NDA, irrespective of the SPA. Moreover, executing the Light Study may be challenging. For example, we may not have randomized a sufficient number of patients with the needed risk profile into the Light Study, the patients we have randomized into the Light Study may not result in the predicted MACE rate, or more trial data than expected may be missed due to loss to follow up of patients in the Light Study. Although diligent attempts are being made to minimize missing data in the Light Study, significant amounts of missing data due to patients who are lost to follow-up may compromise the conduct of the study and the integrity of the analyses. Missing data could also decrease the observed rate of MACE should MACE occur in patients lost to follow up. Either or all of these could delay the interim data analysis and ultimately potential approval.

With respect to Empatic, in September 2009, we announced the results of our latest Phase IIb clinical trial which we believe established that the combination of Empatic's components is more effective than the individual components. It is not clear what magnitude of superiority the FDA will require Empatic to demonstrate versus the most active individual component in order to agree that Phase III clinical trials may be conducted against placebo only. In addition, Empatic contains bupropion, the same active ingredient that gave rise to the FDA's concerns regarding the cardiovascular safety profile of Contrave, which depending on the result of the NDA for Contrave and any additional studies we conduct for it, as well as the FDA's interpretation of the input received from the March 2012 EMDAC meeting, may adversely affect the development of Empatic. In addition, the FDA has provided guidance regarding the observed teratogenic effects of zonisamide and the Phase III trials for Empatic. The FDA stated that women of child bearing potential who have a BMI of $\geq$ 35 kg/m2 accompanied by at least one obesity-related comorbidity has sufficiently high risk from their excess body weight should participate in the Phase III trials. In our recent series of discussions with the FDA on the continued development of Empatic, the FDA stated that Phase III data for Empatic may be sufficient to support submission of an NDA without data from a cardiovascular outcomes trial. The FDA indicated that as long as the placebo-subtracted changes in body weight, blood pressure and heart rate for Empatic are similar to or more favorable than the placebo-subtracted changes observed with Contrave, and there are no signals of cardiovascular concern in the Empatic development program, reassuring results of a cardiovascular outcomes trial with Contrave will be sufficient. In addition, while the FDA reiterated its belief that the preclinical teratogenicity data for zonisamide and the pregnancy outcome data with Empatic from the Phase II clinical trials are very concerning, it will allow Phase III studies of Empatic to include women of childbearing potential with a body mass index, or BMI, >27kg/m^2 in the presence of at least one weight-related comorbidity such as hypertension, type 2 diabetes mellitus or dyslipidemia and a BMI >30 kg/m^2 without additional restrictions if appropriate safety measures and adequate informed consent are provided. The FDA noted that similar safety measures and understanding of risk in the Phase III trials may need to be applied in the intended marketed population if Empatic is approved. The FDA added that additional worrisome pregnancy outcome data in the Empatic trials may have an impact on approvability, labeling or REMS. However, we can provide no assurance that such guidance by the FDA related to Empatic will not change prior to or during any continued development of Empatic.

In addition, we may need to complete additional preclinical testing of our product candidates to evaluate safety and toxicity and the FDA may require us to conduct additional clinical trials. The results from the preclinical and clinical trials that we have completed for Contrave and Empatic may not be replicated in future trials, or we may be unable to demonstrate sufficient safety and efficacy to obtain the requisite regulatory approvals for either product candidate. A number of companies in the biotechnology and pharmaceutical industries have suffered significant setbacks in advanced clinical trials, even after promising results in earlier trials. If our drug candidates are not shown to be safe and effective in clinical trials, our clinical development programs could be delayed or terminated. Any delays could also result in the need for additional financing, and our failure to adequately demonstrate the efficacy and safety of Contrave, Empatic or any other product candidates that we may develop, in-license or acquire would prevent receipt of regulatory approval and, ultimately, the commercialization of that product candidate.

Delays in the commencement or completion of clinical trials, including the Light Study, or the requirement to conduct additional clinical trials could result in increased costs to us and delay or limit our ability to continue development programs and/or generate revenues.

Delays in the commencement or completion of clinical trials, including the Light Study, could significantly affect our product development costs. We do not know whether clinical trials will begin on time or whether clinical trials, including the Light Study, will be completed on schedule, if at all. The commencement and completion of clinical trials, including the Light Study, can be delayed for a number of reasons, including delays related to:

- obtaining regulatory approval to commence a clinical trial, including regulatory approval of the design of a clinical trial;

- reaching agreement on acceptable terms with prospective contract research organizations, or CROs, and trial sites, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and trial sites;
- manufacturing sufficient quantities of a product candidate for use in clinical trials;
- obtaining institutional review board, or IRB, approval to conduct a clinical trial at a prospective site;
- recruiting and enrolling patients to participate in clinical trials for a variety of reasons, including competition from other clinical trial programs for the treatment of obesity or similar indications and the restrictions imposed by the design and length of a clinical trial, including randomizing patients with the needed risk profile with respect to the Light Study;
- retaining patients who have initiated a clinical trial, including the Light Study, but may be prone to withdraw due to side effects from the therapy, lack of efficacy or personal issues, or who are lost to further follow-up;
- the status of our collaborative relationship with Takeda with respect to any additional clinical trials required for Contrave; and
- collecting, reviewing and analyzing our clinical trial data.

Clinical trials, including the Light Study, may also be delayed as a result of ambiguous or negative interim results. In addition, a clinical trial, including the Light Study, may be suspended or terminated by us, a collaborative partner, the FDA, the IRB overseeing the clinical trial at issue, any of our clinical trial sites with respect to that site, or other regulatory authorities due to a number of factors, including:

- failure to conduct the clinical trial in accordance with regulatory requirements or our clinical protocols;
- lack of adequate funding or other resources to continue the clinical trial;
- inspection of the clinical trial operations or trial sites by the FDA or other regulatory authorities resulting in the imposition of a clinical hold;
- unforeseen safety issues; and
- logistical and operational challenges inherent in complex clinical trials.

Additionally, changes in regulatory requirements and guidance for developing products for weight management may occur and we may need to initiate new clinical trials or change protocols of existing clinical trials to account for these changes. For instance, based on the FDA's interpretation of the input received from the March 2012 EMDAC meeting, the FDA may issue final guidance on developing products for weight management. While we believe the designs of our pivotal clinical trials for Contrave and the design for the Light Study are consistent with the current recommendations made by the FDA in the draft guidance, we cannot guarantee that the FDA will not require different or additional clinical trials or studies to support regulatory approval in addition to the Light Study. In addition, many of the factors that cause, or lead to, a delay in the commencement or completion of clinical trials, including the Light Study, may also ultimately lead to the termination of a development program and/or the denial of regulatory approval of a product candidate, including the denial of the Contrave NDA.

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. Contrave has been evaluated in four completed Phase III clinical trials, which we refer to collectively as the Contrave Obesity Research, or COR, program.

Across the entire COR program, seven patients experienced serious adverse events that were attributed by investigators as possibly related or related to Contrave treatment. These include cholecystitis (gallbladder inflammation) (2), seizure (2), palpitations (1), paresthesia (1) and vertigo (1). The most frequently observed treatment-emergent adverse events were nausea, constipation, vomiting and dizziness. Nausea was the leading adverse event resulting in discontinuation; however, for the majority of patients experiencing nausea, it was mild to moderate, transient and manageable. In September 2009, we announced the results from our latest Phase IIb clinical trial for Empatic. The most frequent side effects observed in this clinical trial were headache, nausea and insomnia. Adverse events and laboratory findings appeared to be consistent with the individual components of Empatic, bupropion and zonisamide. Specifically, infrequent reports of idiopathic neutropenia, or transient extremely low white blood cell counts, were observed. Sulfonamides, of which zonisamide belongs, are one of many classes of drugs which have been reported to infrequently cause benign, idiopathic neutropenia.

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. Serious adverse events have been reported to the FDA and study investigators as required in accordance with current guidelines and standards. Serious adverse events that are not characterized by clinical investigators as possibly related to our study drug or adverse events 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 adverse events 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. The FDA may not agree with our methods of analysis or our interpretation of the results.

In addition, the constituent drugs of each of our product candidates each has its own side effect profile that is included in the respective current product label. If our product candidates are approved by the FDA, we would anticipate that their labels would include the side effect profiles of each of the constituent drugs. Moreover, patients in our clinical trials may experience side effects that are indicated in the constituent drugs' labels, as was the case with the side effects experienced by patients in our clinical trials of Contrave and Empatic to date. In addition, while the constituent drugs that make up Contrave and Empatic have post-marketing safety records and while we have tested these constituent drugs in combination in our clinical trials of Contrave and Empatic to date, the safety of the combined use of the constituents of Contrave and Empatic is not yet fully known, and any future trials may produce side effects not observed to date. For example, the Light Study may demonstrate that the risk of MACE in overweight and obese patients treated with Contrave adversely affects the drug's benefit-risk profile and could delay or prevent the regulatory approval of Contrave. In addition, in the Light Study the incidence of known side effects may occur at increased rates or new undesirable side effects may arise that could delay or prevent the regulatory approval of Contrave. The approvability and eventual labeling of Contrave and Empatic will be determined by the safety experience with the drugs in the context of their relative merits (efficacy) in an obese population. Any of the side effects of Contrave or Empatic, or their individual constituent drugs, could delay or prevent their regulatory approval or limit the commercial profile of an approved label.

Further, if any of our product candidates receives marketing approval and we or others, including our collaborative partner, 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 with Contrave or Empatic 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 or our collaborative partner 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 and our collaborative partner 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 and our collaborative partner's ability to successfully commercialize our product candidates and generate revenues.

We rely primarily on third parties to assist us in the preparation of our regulatory applications and conduct our clinical trials. 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 our product candidates within our expected timeframes or at all.

We are currently working with a number of CROs for monitoring, oversight and statistical support for the Light Study. In addition, we expect to use a CRO to assist us with the development of Empatic and the preparation of the regulatory submissions for our product candidates. The third parties with whom we contract for preparation of our regulatory applications and execution of our clinical trials play a significant role in the preparation of regulatory applications, the conduct of our clinical trials and the subsequent collection, review and analysis of data. These third parties, including CROs and investigators, are not our employees, and we have limited ability to control the amount or timing of resources that they devote to our programs. If our CROs, consultants or independent investigators fail to devote sufficient time and resources to our drug development programs and related regulatory applications, or if their performance is substandard, it may delay the potential approval of our regulatory applications and the commercialization of our product candidates. In addition, the execution of clinical trials, the subsequent compilation, review and analysis of the data produced and the preparation of regulatory applications requires coordination among various parties. In order for these functions to be carried out effectively and efficiently, it is imperative that these parties provide the necessary resources and communicate and coordinate with one another. If these third parties are unable to provide the necessary resources or coordinate and communicate with one another, our clinical trials may be delayed or the completion and analysis of the data and the related regulatory applications may be delayed or compromised. Moreover, these third parties may also have relationships with other commercial entities, some of which may compete with us. If these third parties also contract to provide services for our competitors, it could adversely affect our business.

If the contract manufacturers upon whom we rely fail to produce our product candidates in the volumes that we and our current and any future collaborative partner require on a timely basis, or fail to comply with stringent regulations applicable to pharmaceutical drug manufacturers, we and such collaborative partner may face delays in the development and commercialization of our product candidates.

We do not currently possess nor do we plan to implement manufacturing processes internally. We currently utilize the services of contract manufacturers to manufacture our clinical supplies. These clinical supplies include the formulations of our product candidates' active pharmaceutical ingredients, or API, from our API suppliers, the tablets combining those components and the bottles used to package these tablets for use in clinical trials. If the contract manufacturers upon whom we rely fail to produce our product candidates in the volumes required on a timely basis, we may face delays in the development of our product candidate.

In March 2010, we entered into a long-term manufacturing services agreement, or manufacturing agreement, with Patheon Pharmaceuticals and Patheon Inc., which we collectively refer to as Patheon, pursuant to which Patheon has agreed to manufacture commercial quantities of our Contrave tablet products. Under the terms of the manufacturing agreement, we are required to purchase from Patheon a certain percentage of our requirements for Contrave tablet products intended for commercial sale, provided certain terms and conditions are met. The initial term of the manufacturing agreement commenced in March 2010 and shall continue in effect until December 31 st of the year that is five years from the date Contrave first receives approval for marketing from the FDA or any foreign regulatory agencies competent to grant marketing approvals for pharmaceutical products. Upon expiration of the initial term, the agreement will be automatically renewed for additional two year terms. Patheon may terminate the manufacturing agreement at any time upon specified prior written notice to us. We may also terminate the manufacturing agreement with specified prior written notice to Patheon, subject

to our payment of certain termination amounts. Either party may terminate the manufacturing agreement effective immediately upon written notice to the other in the event that (a) the other party dissolves, is declared insolvent or bankrupt by a court of competent jurisdiction, (b) a voluntary petition of bankruptcy is filed in any court of competent jurisdiction, or (c) the manufacturing agreement is assigned for the benefit of creditors. We may terminate the manufacturing agreement upon specified prior written notice if any governmental or regulatory authority, including, but not limited to, the FDA, takes any action, or raises any objection, that prevents us from importing, exporting, purchasing, or selling Contrave tablet products. We are also required to give specified advance notice if we intend to no longer order commercial supplies of Contrave tablet products pursuant to the manufacturing agreement due to the product's discontinuance in the market. Patheon may terminate the manufacturing agreement upon specified prior written notice to us if we assign any of our rights under the manufacturing agreement to an assignee that, in the opinion of Patheon acting reasonably, is (a) not a credit worthy substitute for us, or (b) a competitor of Patheon. Moreover, either party may terminate the manufacturing agreement upon written notice to the other party where the other party has failed to remedy a material breach of any of its representations, warranties, or other obligations under the manufacturing agreement within a specified period of time following receipt of a written notice of the breach, subject to specified terms and conditions.

If we change to other manufacturers in the future, the FDA and comparable foreign regulators must approve these manufacturers' facilities and processes prior to use, which would require new testing and compliance inspections, and the new manufacturers would have to be educated in or demonstrate successful technology transfer of the processes necessary for the production of our product candidates.

The manufacture of pharmaceutical products requires significant expertise and capital investment, including the development of advanced manufacturing techniques and process controls. Manufacturers of pharmaceutical products often encounter difficulties in production, particularly in scaling up for commercial production. These problems include difficulties with production costs and yields, quality control, including stability of the product candidate and quality assurance testing, shortages of qualified personnel and production capacity, equipment failures as well as compliance with strictly enforced federal, state and foreign regulations, which include product requirements established by the FDA or other regulatory agencies and stability requirements in other foreign countries that our current product candidate formulation may not be able to meet. If our manufacturers were to encounter any of these difficulties in the United States or in other foreign countries or otherwise fail to comply with their obligations to us, or if we or our collaborative partner do not accurately forecast our demand, our ability or our collaborative partner's ability to provide product candidates to patients in our and our current and any future collaborative partner's clinical trials, including the Light Study, or to commercially launch a product candidate would be jeopardized. Any delay or interruption in the supply of clinical trial supplies could delay the completion of clinical trials, including the Light Study, increase the costs associated with maintaining a clinical trial program and, depending upon the period of delay, require us or such collaborative partner to commence new trials at significant additional expense or terminate the trials completely.

In addition, all manufacturers of our products must comply with current good manufacturing practice, or cGMP, requirements enforced by the FDA through its facilities inspection program. These requirements include, among other things, quality control, quality assurance and the generation and maintenance of records and documentation. Manufacturers of our products may be unable to comply with these cGMP requirements and with other FDA, state and foreign regulatory requirements. While we have implemented a quality oversight program, we have little control over our manufacturers' compliance with these regulations and standards. A failure to comply with these requirements may result in fines and civil penalties, suspension of production, suspension or delay in product approval, product seizure or recall, or withdrawal of product approval. If the safety of any product supplied is compromised due to our manufacturers' failure to adhere to applicable laws or for other reasons, we may not be able to obtain regulatory approval for or successfully complete the Light Study or any other required clinical trials or commercialize our products, and we may be held liable for any injuries sustained as a result. Any of these factors could cause a delay of clinical trials, including the Light Study, regulatory submissions, approvals or commercialization of our product candidates, entail higher costs or result in our or our

current or any future collaborative partner being unable to effectively commercialize our products. Furthermore, if our manufacturers fail to deliver the required commercial quantities on a timely basis, pursuant to provided specifications and at commercially reasonable prices, we and our current and any future collaborative partner may be unable to meet demand for our products and would lose potential revenues.

There are labeled adverse side effects to the individual use of bupropion, naltrexone and zonisamide.

A key constituent of Contrave and Empatic is bupropion, which has been approved by the FDA for the treatment of depression and to assist smoking cessation. The FDA has directed manufacturers of all antidepressant drugs to include in their product labels a "boxed" warning and expanded warning statements regarding an increased risk of suicidal thinking and behavior in children and adolescents being treated with these drugs. The package insert for bupropion includes such a "boxed" warning statement. In December 2006, the FDA held an advisory committee meeting regarding suicidal thinking and behavior in adults being treated with antidepressant drugs. The advisory committee recommended that the "boxed" warning be extended to cover adults up to their mid-20's. To the extent that any additional warnings or labeling changes related to suicidal thinking and behavior in adults are required, we expect that any such additional warnings or other labeling changes will also be required on labeling for both Contrave and Empatic, if approved. In July 2009, the FDA issued a news release announcing that it was requiring manufacturers to put a "boxed" warning on the prescribing information for smoking cessation drugs including Zyban®, which is a branded form of bupropion. The warning highlights the risk of serious mental health events including changes in behavior, depressed mood, hostility, and suicidal thoughts. Although neither Contrave nor Empatic is intended to be promoted for or used in the treatment of major depression or smoking cessation, we expect that a similar warning statement will be required on labeling for both Contrave and Empatic, particularly because it is likely that there will be obese patients who smoke or depressed obese patients who will use these product candidates, if approved.

The FDA has also directed manufacturers of antidepressant drugs to create Medication Guides to be distributed to patients regarding the risk of suicidal thinking and behavior in children and adolescents. Although we have not included children or adolescents in either the Contrave or Empatic clinical trials, it is possible that the FDA will require a Medication Guide for both Contrave and Empatic. These warnings and other requirements may have the effect of limiting the market acceptance by our current and any future collaborative partner's targeted physicians and patients of Contrave and Empatic, if these product candidates are approved.

The other constituent of Contrave, naltrexone, has been approved by the FDA for the treatment of alcohol and opioid dependence. The FDA has directed the manufacturers of naltrexone for these indications to include in their product labels a "boxed" warning and expanded warnings statements regarding hepatotoxicity, or liver toxicity. A similar warning statement may be required on labeling for Contrave, if approved.

Each of the constituent drugs included in the Contrave and Empatic combinations has in its package insert a "Category C" pregnancy precaution. This means that animal studies have shown that each of these constituent drugs has the potential to cause birth defects and that there have been no adequate and well-controlled studies of the constituent drugs in pregnant women, but that the FDA has determined that the benefits from the use of such drugs in pregnant women may be acceptable despite the potential risks. In addition, although Contrave is not known to be teratogenic, it appears from a recent FDA action, in which the FDA stated that weight loss offers no potential benefit to a pregnant woman and may result in fetal harm, that the FDA is likely to classify all weight loss pharmaceutical products as Category X.

Zonisamide, a constituent drug of Empatic, also has a warning that women of childbearing age should be advised to use contraception due to the teratogenicity seen in animal studies. In addition, because of concerns published in academic journals regarding the possible developmental effects of zonisamide in animals as well as reports from Japan in which women receiving zonisamide combined with other anticonvulsants had children with birth defects, it is likely that Empatic, if approved, will receive a "Category X" pregnancy precaution and thus, would be contraindicated for use by pregnant or nursing women with warnings about use of Empatic in women

of childbearing age. This means that there could be a labeling limitation or REMS on the use of Empatic without adequate contraception or perhaps a prohibition on the use of Empatic by all women of childbearing age. Although we have designed our clinical trials to educate women about the necessity of using adequate contraception while taking, and for a period of time after taking, our product candidates, women may not take the necessary precautions to prevent pregnancy and as a result, women taking our product candidates may risk bearing children with birth defects. For example, during the first Phase IIb trial, four women on Empatic became pregnant and carried the pregnancies to term. Three of the pregnancies resulted in normal infants at birth. In the fourth case there were birth abnormalities, one of which, a cardiac abnormality, was corrected surgically. Although this case is a complicated one with a number of plausible, alternative etiologies, it has been reported by the investigator as a serious adverse event and possibly related to Empatic. Sulfonamides, of which zonisamide belongs, are one of many classes of drugs which have been reported to infrequently cause benign, idiopathic neutropenia, or transient extremely low white blood cell counts. Infrequent reports of idiopathic neutropenia were observed in our Empatic Phase IIb trial.

The FDA has issued an alert based on updated clinical data that treatment with zonisamide can cause metabolic acidosis in some patients. Metabolic acidosis is a disturbance in the body's acid-base balance that results in excessive acidity in the blood. The FDA recommended that healthcare professionals monitor for metabolic acidosis at the start of treatment with zonisamide and periodically during treatment with zonisamide even in the absence of symptoms. We have been monitoring for metabolic acidosis in all of our Empatic clinical trials, and we have not observed any clinically meaningful cases of metabolic acidosis. A warning statement about metabolic acidosis may be required in the labeling for Empatic.

The FDA has analyzed reports of suicidal behavior or ideation from placebo-controlled clinical studies of eleven anticonvulsants (including zonisamide). In the FDA's analysis, patients receiving anticonvulsants had approximately twice the risk of suicidal behavior or ideation compared to patients receiving placebo. The relative risk for suicidal behavior or ideation was higher in the patients with epilepsy compared to patients who were given one of the anticonvulsants for conditions other than epilepsy. The FDA has indicated that it will be working with manufacturers of marketed anticonvulsants to include this new information in the labeling of these products. It is possible that any changes related to suicidal behavior or ideation that occur to the labels of these anticonvulsants will be required on the labeling for Empatic, if approved.

Notwithstanding the existing labeling for the constituents of our drugs in development, the FDA may choose to apply more stringent warning statements or stronger classifications or categorizations of risk in the labeling for Contrave or Empatic, if approved, based on the different risk-benefit profile of our product candidates in the context of unmet need in the treatment of obesity, as compared to the approved indications for the constituent drugs of Contrave and Empatic. For example, the label ultimately approved for Contrave or Empatic, if any, may include restrictions on use that may not appear in the existing labeling for the constituent drugs in Contrave or Empatic, including restrictions based on pregnancy status, level of obesity and duration of treatment or a "boxed" warning consistent with those for antidepressants, anticonvulsants, products for smoking cessation, naltrexone or otherwise.

Any of these known side effects and any associated warning statements or classification or categorization of risk may limit the commercial profile of an approved label for our product candidates and prevent us or our collaborative partner from achieving or maintaining market acceptance of our product candidates.

The CRL we received for the Contrave NDA may also materially and adversely affect our Empatic development program.

Empatic contains bupropion, the same active ingredient that gave rise to the FDA's concerns regarding the cardiovascular safety profile of Contrave. We are unable to predict whether the FDA may extend the requirement to conduct a CVOT to Empatic as well or whether the March 2012 EMDAC meeting will result in other such requirements. In our recent series of discussions with the FDA on the continued development of Empatic, the

FDA stated that Phase III data for Empatic may be sufficient to support submission of an NDA without data from a CVOT. The FDA indicated that as long as the placebo-subtracted changes in body weight, blood pressure and heart rate for Empatic are similar to or more favorable than the placebo-subtracted changes observed with Contrave, and there are no signals of cardiovascular concern in the Empatic development program, reassuring results of a CVOT with Contrave will be sufficient. The evidence we gather from the Light Study, however, may not demonstrate that Contrave is safe and effective for use in our target indication and, moreover, may demonstrate that the risk of adverse cardiovascular events in overweight and obese patients treated with Contrave adversely affects the drug's benefit-risk profile. Such a result could not only delay or terminate our development program for Contrave, but Empatic as well, which could result in our inability to continue operations because we currently have no additional product candidates in development.

Even if our product candidates receive regulatory approval, they may still face future development and regulatory difficulties.

Even if U.S. regulatory approval is obtained, the FDA may still impose significant restrictions on a product's indicated uses or marketing or impose ongoing requirements for potentially costly post-approval studies. For example, the label ultimately approved for Contrave or Empatic, if any, may include restrictions on use, including restrictions based on pregnancy status, level of obesity and duration of treatment or a "boxed" warning consistent with those for antidepressants, anticonvulsants, products for smoking cessation, naltrexone or otherwise. We submitted a REMS to the FDA as part of our NDA for Contrave. The FDA may require a more restrictive REMS. Our product candidates will also be subject to ongoing FDA requirements governing the labeling, packaging, storage, advertising, promotion, recordkeeping and submission of safety and other post-market information. In addition, we are unable to predict whether the FDA may require a CVOT for Empatic or if the FDA will request additional clinical trials be conducted after either product candidate receives regulatory approval. We may not have the resources to conduct such additional clinical trials, if required, and our ability to comply with the FDA requirements may be negatively impacted.

Manufacturers of drug products and their facilities are also subject to continual review and periodic inspections by the FDA and other regulatory authorities for compliance with cGMP regulations. If we, a collaborative partner or a regulatory agency discover previously unknown problems with a product, such as adverse events of unanticipated severity or frequency, or problems with the facility where the product is manufactured (including a change or revision to the specifications set forth in the facility's drug master file, or DMF), a regulatory agency may impose restrictions on that product, the manufacturer, our collaborative partner or us, including requiring withdrawal of the product from the market or suspension of manufacturing. If we, a collaborative partner, our product candidates or the manufacturing facilities for our product candidates fail to comply with applicable regulatory requirements, a regulatory agency may:

- issue Warning Letters or untitled letters;
- impose civil or criminal penalties;
- suspend regulatory approval;
- suspend any ongoing clinical trials, including the Light Study;
- refuse to approve pending applications or supplements to applications filed by us;
- impose restrictions on operations, including costly new manufacturing requirements; or
- seize or detain products or require us or our collaborative partner to initiate a product recall.

If the suppliers upon whom we rely for API fail to produce such ingredients in the volumes that we or our collaborative partner require on a timely basis, or to comply with stringent regulations applicable to pharmaceutical drug manufacturers, we or our collaborative partner may face delays in the development or commercial launch of our product candidates.

We do not manufacture any of our API nor do we plan to develop any capacity to do so. Instead, we rely on suppliers of API to provide component materials to our other contract manufacturers, who produce finished pharmaceutical products incorporating the API. The failure or inability of our API suppliers to satisfy our API requirements on a timely basis could delay our development programs, including the Light Study, or commercial launch of our product candidates, if approved.

Although naltrexone itself is not addictive, synthesis of naltrexone is a multi-step process with a natural opiate starting material that has the potential for abuse and is therefore regulated as a controlled substance under the federal Controlled Substances Act or applicable foreign equivalents. As such, manufacturers of naltrexone API must be registered with the Drug Enforcement Administration, or DEA, or applicable foreign equivalents. Manufacturers making naltrexone also must obtain annual quotas from the DEA for the opiate starting material. Because of the DEA-related requirements and modest current demand for naltrexone API, there currently exist a limited number of manufacturers of this API. Therefore, API costs for naltrexone are greater than for the other constituents of our product candidates. Demand for Contrave may require amounts of naltrexone greater than the currently available worldwide supply or our or our collaborative partner's current forecasts for the supply to us of Contrave or its components. Any lack of sufficient quantities of naltrexone would limit our or our collaborative partner's ability to complete any additional required clinical trials, including the Light Study, and to launch and continue to commercialize Contrave. Although we are evaluating additional possible manufacturers to supplement our current naltrexone manufacturing capacity, including those in the United States, Europe and Asia, we may not be successful in accessing additional manufacturing supply of naltrexone API or other necessary components of our product candidates at the appropriate quantities, quality or price.

We have entered into long-term supply agreements for the supply of naltrexone and bupropion API. In January 2009, we entered into a supply agreement with Cilag AG, pursuant to which Cilag will manufacture commercial supplies of naltrexone for use in our drug products. The supply agreement shall continue in effect until four years from the period beginning on the first December 31 st following marketing approval by the FDA for a drug product of ours containing naltrexone. Either party may terminate the supply agreement effective immediately upon written notice to the other in the event that (a) the other party dissolves, is declared insolvent or bankrupt by a court of competent jurisdiction, (b) a voluntary or involuntary petition of bankruptcy is filed in any court of competent jurisdiction, or (c) the supply agreement is assigned for the benefit of creditors. In addition, we may terminate the supply agreement effective immediately upon written notice in the event that (a) any regulatory agency takes any action, or raises any objection that prevents us from importing, exporting, purchasing or selling a finished product containing naltrexone, (b) the product containing naltrexone fails during clinical trials and we withdraw our NDA, (c) we determine, in our sole discretion, to no longer pursue the development and/or commercialization of a product containing naltrexone, or (d) a legal proceeding shall be instituted against Cilag, which is reasonably likely to materially adversely affect Cilag's ability to properly perform under the supply agreement or subject us to any material risk of liability or loss. Moreover, either party may terminate the agreement upon specified written notice of a failure by the other party to perform or observe any material covenant, condition or agreement to be performed or observed by it under the supply agreement, unless such breach has been cured within the specified notice period.

In December 2009, we entered into a supply agreement with Chemi, S.p.A, pursuant to which Chemi will manufacture commercial supplies of bupropion for use in our drug products. The initial term of the supply agreement commenced retroactively in November 2009 and shall continue in effect until the date that is four years from the date we first receive marketing approval from the FDA or other governmental agency, or similar regulatory agency or commission in any foreign state or territory for our drug product containing bupropion. This initial term shall be automatically renewed for additional two year terms unless we provide specified written notice of our intent to terminate to Chemi prior to the expiration of the initial term or any extension term, as

applicable. Either party may terminate the supply agreement effective immediately upon written notice to the other in the event that (a) the other party dissolves, is declared insolvent or bankrupt by a court of competent jurisdiction, (b) a voluntary or involuntary petition of bankruptcy is filed in any court of competent jurisdiction, (c) the supply agreement is assigned for the benefit of creditors, (d) any regulatory agency takes any action, or raises any objection that prevents us from importing, exporting, purchasing or selling bupropion or our drug product containing bupropion, (e) our drug product containing bupropion fails during clinical trials and we withdraw our NDA, (f) we determine, in our sole discretion, to no longer pursue the development and/or commercialization of our drug product containing bupropion, or (g) a legal proceeding shall be instituted against Chemi, which is reasonably likely to materially adversely affect Chemi's ability to properly perform under the supply agreement or subject us to any material risk of liability or loss. Moreover, either party may terminate the supply agreement upon specified written notice to the other party of a failure by that party to perform or observe any material covenant, condition or agreement to be performed or observed by it under the supply agreement, unless such breach has been cured within the specified notice period.

We have no other material long-term commitments or supply agreements with any of our other API suppliers. Although we may seek to establish additional long-term supply commitments in the future, we may be required to agree to minimum volume requirements, exclusivity arrangements or other restrictions. We may not be able to enter into additional long-term agreements on commercially reasonable terms, or at all. Consequently, even if and when our product candidates are approved, we and our current and any future collaborative partner may not be able to successfully commercialize these product candidates if we are unable to secure long-term supply commitments for all of their API components.

In addition, our API suppliers must comply with cGMP requirements enforced by the FDA through its facilities inspection program and must maintain and comply with their respective DMFs on file with the FDA. These requirements include, among other things, quality control, quality assurance and the generation and maintenance of records and documentation. Suppliers of our API may be unable to comply with these cGMP requirements and with other FDA, state and foreign regulatory requirements. While we have implemented a quality oversight program, we have little control over our manufacturers' compliance with these regulations and standards. A failure to comply with these requirements may result in fines and civil penalties, suspension of production, suspension or delay in product approval, product seizure or recall, or withdrawal of product approval. If the safety of any product supplied is compromised due to our suppliers' failure to adhere to applicable laws or for other reasons, we may not be able to obtain regulatory approval for or successfully commercialize our products, and we may be held liable for any injuries sustained as a result. Any of these factors could cause a delay of clinical trials, including the Light Study, regulatory submissions, approvals or commercialization of our product candidates, entail higher costs or result in our and our current and any future collaborative partner being unable to effectively commercialize our products. Furthermore, if our suppliers fail to deliver the required commercial quantities of API on a timely basis, pursuant to the required specifications set forth in their respective DMF and at commercially reasonable prices, and we are unable to timely secure and qualify additional suppliers with applicable regulatory authorities, we and our current or any future collaborative partner may not be able to successfully commercialize our product candidates, any commercial launch could be delayed and/or we and such collaborative partner may be unable to meet demand for our products and would lose potential revenues.

We are dependent on our collaboration with Takeda to commercialize Contrave in the United States, Canada and Mexico, and, if our NDA for Contrave is approved by the FDA, to further develop Contrave. This collaboration may place the commercialization and, if applicable, the development outside our control, and poor performance under or failure to maintain the collaboration agreement between us and Takeda could have a material and adverse impact on our business.

In September 2010, we entered into a collaboration agreement with Takeda for the development and commercialization of Contrave in the United States, Canada and Mexico. We cannot be certain that our collaboration with Takeda will continue, particularly in light of the substantial additional development

requirements in order to resubmit an NDA for Contrave. Both we and Takeda have the right to terminate the collaboration agreement, in certain circumstances, prior to its expiration, including a right by Takeda to terminate the agreement upon specified prior written notice. If the agreement is terminated prior to its expiration, we may not be able to find another collaborator for the development and commercialization of Contrave, and even if we elected to pursue further development and commercialization of Contrave on our own, we might not be able to do so successfully and would experience substantially increased capital requirements that we might not be able to fund.

Our dependence on Takeda and the collaboration agreement will subject us to a number of risks, including:

- Takeda may not perform as expected and we may not be able to control the amount and timing of resources that Takeda may devote to the post-approval development or commercialization of Contrave;
- we and Takeda could disagree as to pre-approval or post-approval development plans and Takeda may delay clinical trials, including the Light Study, or stop a clinical trial, including the Light Study;
- there may be disputes between us and Takeda, including disagreements regarding the collaboration agreement, that may result in (a) the delay of (or prevent entirely) the achievement of regulatory and commercial objectives that would result in milestone payments, (b) the delay or termination of the development or commercialization of Contrave, and/or (c) costly litigation or arbitration that diverts our management's attention and resources;
- Takeda may not comply with applicable regulatory guidelines with respect to developing or commercializing Contrave, which could adversely impact the development of or sales of Contrave and could result in administrative or judicially imposed sanctions, including warning letters, civil and criminal penalties, injunctions, product seizures or detention, product recalls, total or partial suspension of production and refusal to approve any new drug applications;
- Takeda may not provide us with timely and accurate information regarding sales activities and supply forecasts, which could adversely impact our ability to comply with our manufacturing and supply obligations under the collaboration agreement and our and Takeda's ability to launch and commercialize Contrave, if approved;
- Takeda may experience financial difficulties;
- business combinations or significant changes in Takeda's business strategy may also adversely affect Takeda's ability to perform its obligations under our collaboration agreement;
- Takeda may not properly maintain or defend our intellectual property rights or may use our proprietary information in such a way as to invite litigation that could jeopardize or invalidate our proprietary information or expose us to potential litigation; and
- notwithstanding the non-competition requirements in the collaboration agreement, Takeda could independently move forward with a competing product candidate developed either independently or in collaboration with others, including our competitors.

Any failure of Takeda to adequately perform its obligations under our collaboration agreement or the termination of such agreement could have a material and adverse impact on our business.

We expect intense competition in the obesity marketplace for Contrave and Empatic, if approved, and new products may emerge that provide different or better therapeutic alternatives for obesity and weight loss.

If approved and commercialized, both Contrave and Empatic will compete with well established prescription drugs for the treatment of obesity, including Xenical® (orlistat), marketed by Genentech, Inc. Orlistat has also been launched by GlaxoSmithKline in over-the-counter form under the brand name allí®, which represents additional competition and potential negative pricing pressure. Orlistat is marketed by a pharmaceutical company with substantially greater resources than we have. In addition, a number of generic

pharmaceutical products are prescribed for obesity, including phentermine, phendimetrazine, benzphetamine and diethylpropion. Some of these generic drugs, and others, are prescribed in combinations that have shown anecdotal evidence of efficacy. These products are sold at much lower prices than we or our collaborative partner intend to charge for our product candidates, if approved. The availability of a large number of branded prescription products, including drugs that are prescribed off-label, generic products and over-the-counter products could limit the demand for, and the price we or our collaborative partner are able to charge for, our product candidates. In addition, in June 2012, Arena Pharmaceuticals, Inc., or Arena, obtained FDA approval for its product, locaserin, which it has indicated will be marketed, once launched, in the United States under the name Belviq. In July 2012, Vivus, Inc. obtained FDA approval for its combination product, phentermine/topiramate. Vivus commercially launched its combination product in the United States under the name Qsymia in September 2012. Vivus, and Arena, if Arena or its partner Eisai Pharmaceuticals, Inc. commercially launches Belviq, may build a significant competitive advantage prior to the time we and our collaborative partner are able to market Contrave, or we or any future collaborative partner are able to market Empatic, if approved. Further, if safety concerns about these products' use arise after their launch, such concerns may materially and adversely affect the labeling for Contrave or Empatic and/or our ability to gain approval of the NDA for Contrave or Empatic and, if approved, our and our collaborative partner's ability to effectively market and sell Contrave or Empatic. If such products are successfully marketed, they could represent additional competition and potential negative pricing pressure with respect to Contrave or Empatic.

Currently, there are a number of drug products in development for obesity which could become competitors against our product candidates. These include products being developed by Athersys, Inc., Bristol-Myers Squibb, Neurosearch A/S, Norgine BV, Novo Nordisk A/S, our partner, Takeda, and Zafgen, Inc.

There are also surgical approaches to treat severe obesity that are becoming increasingly accepted and could become competitors against our product candidates. Two of the most well established surgical procedures are gastric bypass surgery and adjustable gastric banding. In addition, other potential approaches which utilize various implantable devices or surgical tools are in development, including an endoscopic approach for treating obesity. Some of these approaches are in late stage development and may be approved for marketing. Companies such as Allergan, Inc., Boston Scientific, Covidien Ltd., EnteroMedics, Inc., GI Dynamics, Inc., Johnson & Johnson, and Medtronic, Inc. are all active in this space and may have substantially greater resources than we have.

New developments, including the development of other drug technologies and methods of preventing the incidence of disease, occur in the nutritional, pharmaceutical and medical technology industries at a rapid pace. These developments may render our product candidates less competitive. Some of our potential competitors are large pharmaceutical or device firms and have substantially greater resources than we have. These resources could be directed toward the obesity market and include:

- research and development resources, including personnel and technology;
- regulatory experience;
- drug development and clinical trial experience;
- experience and expertise in exploitation of intellectual property rights; and
- capital resources.

As a result of these factors, our competitors may obtain regulatory approval of their products more rapidly than we do or may obtain patent protection or other intellectual property rights that limit our ability to develop or commercialize our product candidates. Our competitors may also develop drugs or surgical approaches that are more effective, more useful and less costly than ours and may also be more successful in manufacturing and marketing their products. In addition, our competitors may be more effective in commercializing their products. We currently outsource our manufacturing and therefore rely on third parties for that competitive expertise. There can be no assurance that we will be able to develop or contract for these capabilities on acceptable

economic terms, or at all. In addition, should both Contrave and Empatic be approved to treat obesity, these product candidates may compete with one another. While we intend to direct each product candidate to specific segments of the obesity marketplace, the FDA does not distinguish between these types of obesity and, if approved, any potential label for Contrave and Empatic would be expected to refer to obesity generally. There is no guarantee that we and our current and any future collaborative partner will be successful in marketing Contrave and Empatic to their respective target markets, if approved, or minimizing competition between them.

Our product candidates are combinations of generically-available pharmaceutical products, and our success is dependent on our ability and our collaborative partner's ability to compete against off-label generic substitutes and demonstrate the advantages of our proprietary combination products.

Off-label use occurs when physicians prescribe a drug that is approved by the FDA for one indication for a different, unapproved indication. We believe that a practitioner seeking safe and effective therapy is not likely to prescribe such off-label generics in place of Contrave or Empatic because the dosage strengths, pharmacokinetic profiles and titration regimens recommended for Contrave and Empatic are not available using existing generic preparations of immediate release, or IR, naltrexone, zonisamide IR and bupropion SR, and there are no oral generic SR formulations of naltrexone or zonisamide. However, a physician could seek to prescribe off-label generics in place of Contrave or Empatic. Such off-label prescriptions could significantly diminish the market potential of our products and significantly impact our ability and our collaborative partner's ability to generate revenues.

With regard to off-label substitution at the pharmacy level, we expect to rely on the novel dose ratios and novel pharmacokinetic properties of our product candidates, as well as the differences in their approved indications, to provide sufficient distinction such that generic preparations are not considered therapeutic equivalents by the FDA. State pharmacy laws in many instances only permit pharmacists to substitute generic products for branded products if the products are therapeutic equivalents. Therefore, the lack of therapeutic equivalency should limit generic substitution by pharmacies and/or pharmacy benefit managers. However, we cannot be certain that pharmacists and/or pharmacy benefit managers will not seek prescriber authorization to substitute generics in place of Contrave and Empatic, which could significantly diminish their market potential and significantly impact our ability and our collaborative partner's ability to successfully commercialize our product candidates and generate revenues.

In addition, although we believe the current market prices for the generic forms of naltrexone and zonisamide make generic substitution by physicians, pharmacists or pharmacy benefit managers unlikely, should the prices of the generic forms decline, the motivation for generic substitution may become stronger. Wide scale generic substitution by physicians and at the pharmacy level could have substantial negative consequences to our business.

We have limited sales and marketing experience and resources, and if we do not enter into additional collaboration or co-promotion arrangements, we may not be able to effectively market and sell Contrave outside the United States, Canada or Mexico or Empatic, if approved, and our ability to generate revenues may be delayed or limited.

We are developing our obesity product candidates for large markets traditionally served by general and family practitioners and internists. Generalist physicians number in the several hundred thousand in the United States. Traditional pharmaceutical companies employ groups of sales representatives numbering in the thousands to call on this large generalist physician population. In order to effectively promote to these physician groups, we entered into a collaboration agreement with Takeda in September 2010 to develop and commercialize Contrave in the United States, Canada and Mexico. In order to expand the market opportunity outside of these countries for Contrave and to address the commercialization of Empatic, if approved, we must either establish additional sales and marketing collaborations or co-promotion arrangements or expend significant resources to develop our own sales and marketing presence. We currently possess limited resources and may not be successful in developing

our own sales and marketing presence. We may not be able to enter into additional collaboration or co-promotion arrangements on acceptable terms, if at all. If we are unable to enter into additional collaboration or co-promotion arrangements for Contrave outside the United States, Canada and Mexico or for Empatic, and we must develop our own sales and marketing presence to address the large market of general and family practitioners and internists in these areas, we will require additional capital and our ability to market and sell our product candidates and generate revenues from our product candidates may be delayed or limited. We also face competition in our search for collaborators, co-promoters and sales force personnel. If our competitors are able to establish collaboration or co-promotion arrangements with pharmaceutical companies who have substantially greater resources than we have, our ability to successfully commercialize Contrave outside the United States, Canada and Mexico and/or Empatic will be limited and as a result our competitors may be more successful in marketing and selling their products in these areas. Even if we do enter into additional collaboration or co-promotion arrangements with third parties, we will be reliant on such third parties to successfully develop and/or commercialize our product candidates in these areas. These third parties may fail to develop or effectively commercialize our product candidates because they cannot obtain the necessary regulatory approvals, decide to pursue a competitive potential product that may be developed outside of the collaboration or fail to devote the resources necessary to realize the full commercial potential of our product candidates, especially in light of the resources being devoted by our competitors' collaboration and co-promotion partners. Any such failures would negatively affect our ability to generate revenues from sales of Contrave outside the United States, Canada and Mexico or from sales of Empatic.

Our development and commercialization strategy depends upon access to findings of safety and effectiveness based on data not developed by us but which the FDA may reference in reviewing our U.S. marketing applications. In territories outside the United States, we must either negotiate access to these safety and effectiveness findings or develop them ourselves.

The Drug Price Competition and Patent Term Restoration Act of 1984, also known as the Hatch-Waxman Act, added Section 505(b)(2) to the Federal Food, Drug, and Cosmetic Act. Section 505(b)(2) permits the filing of an NDA where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference. This statutory provision expressly allows the FDA to rely, for purposes of approving an NDA, on findings of safety and effectiveness based on data not developed by the filer of the NDA. Under these guidelines, we were able to move directly into Phase II clinical trials for each of our drug combinations, because our NDA for Contrave would rely, and our planned NDA for Empatic, will rely, in part, upon the FDA's findings of safety and effectiveness for the previously-approved products that are incorporated into Contrave and Empatic. Similar legislation for active substances with well-established medicinal use exists in the European Union under article 10a of European Directive 2001/83/EC, which allows for reference to scientific literature if active substances have been approved for at least ten years. There also are alleviations under article 10b of European Directive 2001/83/EC of the obligation to provide scientific references relating to individual active substances in combination products if such individual active substances have been previously authorized in the European Union, although not the obligation to provide results of new clinical trials relating to such combination products, which could provide an alternative pathway in Europe. In territories where data are not freely available, we may not have the ability to commercialize our products without negotiating rights from third parties to refer to their clinical data in our regulatory applications, which could require the expenditure of significant additional funds to generate our own data. We may be unable to obtain rights to the necessary clinical data and may be required to develop our own proprietary safety and manufacturing dossiers. In addition, even though we can take advantage of Section 505(b)(2) to support potential U.S. approval for Contrave and Empatic, the FDA may also require us to perform additional studies or measurements to support changes from the previously-approved products incorporated into our product candidates.

To the extent that a Section 505(b)(2) application relies on the FDA's finding of safety and effectiveness of a previously-approved drug, the applicant is required to make certifications to the FDA with respect to any patents listed for the approved product in the FDA's publication called "Approved Drug Products with

Therapeutic Equivalence Evaluations," otherwise known as the "Orange Book." Specifically, the applicant must certify when the application is submitted that: (1) there is no relevant patent information listed; (2) the listed patent has expired; (3) the listed patent has not expired, but will expire on a particular date and approval is sought after patent expiration; or (4) the listed patent is invalid or will not be infringed by the manufacture, use, or sale of the new product. A certification that the new product will not infringe the already approved product's Orange Book listed patents or that such patents are invalid is called a paragraph IV certification. If the 505(b)(2) applicant has provided a paragraph IV certification to the FDA, the applicant must also send notice of the paragraph IV certification to the NDA holder and patent owner. We have made paragraph IV certifications that Contrave does not infringe the bupropion SR formulation patents listed in the Orange Book, and have sent the appropriate notice to the patent holder and NDA holder. We will be required to make similar certifications if and when we file an NDA for Empatic. In the event that the patent holder or NDA holder files a patent infringement lawsuit against us within 45 days of its receipt of our paragraph IV certification, such lawsuit would automatically prevent the FDA from approving our Section 505(b)(2) NDA until the earliest of 30 months, expiration of the applicable patent (2013 in the case of bupropion SR), settlement of the lawsuit or a decision in the infringement case that is favorable to us. Any such patent infringement lawsuit could be costly, take a substantial amount of time to resolve and divert management resources. This 45-day period with respect to our certifications related to bupropion SR in Contrave has elapsed and no such lawsuit was filed against us. If we obtain FDA approval for either Contrave or Empatic, we could obtain three years of Hatch-Waxman marketing exclusivity for such product, since we have conducted a substantial clinical program that is essential to approval of our NDA. Under this form of exclusivity, the FDA would be precluded from approving a 505(b)(2) NDA or ANDA for the same drug product for the protected indication (for example, a product that incorporates the change or innovation represented by our product) for a period of three years, although the FDA may accept and commence review of such applications. However, this form of exclusivity might not prevent the FDA from approving a 505(b)(1) NDA that relies on its own clinical data. Further, if another company obtains approval for an identical product candidate for the same indication we are studying before we do, our approval could be blocked until the other company's Hatch-Waxman marketing exclusivity expires.

Even if our product candidates receive regulatory approval in the United States, we may never receive approval or commercialize our products outside of the United States.

In order to market any products outside of the United States, we must establish and comply with numerous and varying regulatory requirements of other countries regarding safety, efficacy and manufacturing. Approval procedures vary among countries and can involve additional product testing and additional administrative review periods. The time required to obtain approval in other countries might differ from that required to obtain FDA approval. The regulatory approval process in other countries may include all of the risks detailed above regarding FDA approval in the United States as well as other risks. Regulatory approval in one country does not ensure regulatory approval in another, but a failure or delay in obtaining regulatory approval in one country may have a negative effect on the regulatory process in others. For example, although Vivus obtained FDA approval for its combination product, phentermine/topiramate, in October 2012, the European Medicines Agency's, or EMA's, Committee for Medicinal Products for Human Use, or CHMP, adopted an opinion recommending against the approval of the marketing authorization application for such product due to concerns about its long-term effects on the heart and blood vessels, particularly due to the effects of the phentermine component, its long-term psychiatric effects (depression and anxiety were reported in the studies) and cognitive effects (such as problems with memory and attention) related to the topiramate component, as well as known risks with topiramate being potentially harmful to the unborn baby if taken by pregnant women. The CHMP also noted that there was a high probability that, if approved, Vivus' product would not be used strictly for the intended patients. Vivus requested a re-examination of the CHMP's opinion. After considering the grounds for this request, the CHMP re-examined the initial opinion, and confirmed the refusal of the marketing authorization in February 2013. Further, according to Vivus, the CHMP indicated that a pre-approval CVOT would be necessary to establish the long-term safety of its product. We may face similar negative recommendations with respect to any regulatory filings we submit for our product candidates in the European Union and other geographies.

We have initiated activities with the EMA to enable submission of a marketing authorization application supporting potential approval of Contrave in the European Union under a centralized procedure. We expect to submit a Contrave marketing authorization around the time of the resubmission of the Contrave NDA. As a result, we are also in the process of establishing an agreed-to pediatric investigation plan, or PIP, with the EMA's Pediatric Committee. However, we can provide no assurance that we will be able to submit a marketing authorization on that timeframe, or at all, whether as a result of our failure to reach agreement on a PIP, or otherwise. Failure to obtain regulatory approval for our product candidates in other countries or any delay or setback in obtaining such approval could have the same adverse effects detailed above regarding FDA approval in the United States. As described above, such effects include the risks that our product candidates may not be approved for all indications requested, which could limit the uses of our product candidates and have an adverse effect on their commercial potential or require costly, post-marketing follow-up studies.

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

The use of our product candidates in clinical trials, including the Light Study, and the sale of any products for which we obtain marketing approval expose us to the risk of product liability claims. Product liability claims might be brought against us by consumers, health-care providers, pharmaceutical companies or others selling or otherwise coming into contact with our products. If we cannot successfully defend ourselves against product liability claims, we could incur substantial liabilities. In addition, regardless of merit or eventual outcome, product liability claims may result in:

- decreased demand for our product candidates;
- impairment of our business reputation;
- withdrawal of clinical trial participants;
- costs of related litigation;
- distraction of management's attention from our primary business;
- substantial monetary awards to patients or other claimants;
- loss of revenues; and
- the inability to commercialize our product candidates.

We have in the past obtained product liability insurance coverage for our clinical trials and we have obtained product liability insurance coverage for the Light Study. Our insurance coverage may not be sufficient to reimburse us for any expenses or losses we may suffer. Moreover, insurance coverage is becoming increasingly expensive, and, 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 due to liability. If and when we obtain marketing approval for any of our product candidates, we intend to expand our insurance coverage to include the sale of commercial products; however, we may be unable to obtain this product liability insurance on commercially reasonable terms. On occasion, large judgments have been awarded in class action lawsuits based on drugs that had unanticipated side effects. A successful product liability claim or series of claims brought against us could cause our stock price to decline and, if judgments exceed our insurance coverage, could decrease our cash and adversely affect our business.

If any of our product candidates for which we receive regulatory approval does not achieve broad market acceptance, the revenues, including any milestone or royalty payments we may be eligible to receive under our collaboration agreement with Takeda, that we generate from their sales will be limited.

The commercial success of our product candidates for which we obtain marketing approval from the FDA or other regulatory authorities will depend upon the acceptance of these products by both the medical community

and patient population. Coverage and reimbursement of our product candidates by third-party payors, including government payors, generally is also necessary for optimal commercial success. The degree of market acceptance of any of our approved products will depend on a number of factors, including:

- our ability to provide acceptable evidence of safety and efficacy;
- the timing of market introduction of our products as well as competitive products;
- the relative convenience and ease of administration;
- the prevalence and severity of any adverse side effects;
- limitations or warnings contained in a product's FDA-approved labeling, including, for example, potential "black box" warnings or pregnancy precautions associated with the APIs in Contrave and/or Empatic;
- availability of alternative treatments and the potential or perceived advantages or disadvantages of such treatments, including, in the case of Contrave and/or Empatic, a number of competitive products already approved for the treatment of weight loss or expected to be commercially launched in the near future;
- pricing and cost effectiveness;
- our REMS;
- the effectiveness of our, or our current or any future collaborators' sales and marketing strategies;
- our and our current or any future collaborative partner's 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 our product candidates are approved but do not achieve an adequate level of acceptance by physicians, health care payors and patients, we may not generate sufficient revenue from these products, and we may not become or remain profitable. In addition, our and our current and any future collaborative partner's efforts to educate the medical community and third-party payors on the benefits of our product candidates may require significant resources and may never be successful.

We and our current and any future collaborative partner are subject to uncertainty relating to reimbursement policies which, if not favorable to our product candidates, could hinder or prevent our product candidates' commercial success.

Our ability and our current and any future collaborative partner's ability to commercialize our product candidates successfully will depend in part on the extent to which governmental authorities, private health insurers and other third-party payors establish appropriate coverage and reimbursement levels for our product candidates and related treatments. As a threshold for coverage and reimbursement, third-party payors generally require that drug products have been approved for marketing by the FDA. Third-party payors also are increasingly challenging the effectiveness of and prices charged for medical products and services. We cannot provide any assurances that we or such collaborative partner will be able to obtain third-party coverage or reimbursement for our product candidates in whole or in part.

The obesity therapy market, in particular, continues to be marked by limited coverage and reimbursement from health insurers and other payors, who have historically viewed obesity as a lifestyle issue. For example, state Medicaid programs, administered by individual states for qualifying low-income individuals, are permitted to exclude coverage for weight loss drugs. In addition, weight loss drugs are excluded from coverage under the Medicare Part D prescription drug program for eligible seniors and disabled individuals. Medicare is a federal governmental third-party payor whose policies often are emulated or adopted by other payors, Although the Centers for Medicare & Medicaid Services, or CMS, which administers the Medicare program, has removed

longstanding policy language that obesity itself cannot be considered an illness, the agency interprets the Part D exclusion of weight loss drugs as applying to novel obesity therapies. However, CMS has since issued a national policy covering bariatric surgery for co-morbid conditions associated with obesity, and in the fourth quarter of 2011 announced that the Medicare program was adding new benefit coverage for prevention with the objective of treating obesity. The new benefit provides for screening for obesity and counseling for eligible beneficiaries by primary care providers in physician's offices. Although third-party payor attitudes regarding obesity-related products and services appear to be changing, as exemplified by Medicare changes, we may continue to face a poor coverage and reimbursement environment.

Currently, our competitors' drug products have limited third-party payor coverage. This means that individuals prescribed such drug products often either have significant out-of-pocket costs or pay for the products entirely by themselves. If our product candidates do not receive adequate coverage or reimbursement, the market acceptance and commercial success of our products may be limited.

Healthcare reform measures could hinder or prevent our product candidates' commercial success.

Among policy makers and payors in the United States and elsewhere, there is significant interest in promoting changes in healthcare systems to contain healthcare costs and improve quality. While reform proposals often involve expanding coverage to more individuals, healthcare reform may also involve increased government price controls, additional regulatory mandates and other measures designed to lower medical and pharmaceutical costs. Within the United States, the pharmaceutical industry has been a particular focus of both the U.S. Congress, as well as state governments.

In March 2010, the President signed into law one of the most significant health reform measures in decades. The Patient Protection and Affordable Care Act, as amended by the Health Care and Education Affordability Reconciliation Act, or collectively the PPACA, substantially changes the way healthcare is financed by both governmental and private insurers, including several payment reforms that establish payments to hospitals and physicians based in part on quality measures, subjects biologic products to potential competition by lower-cost "biosimilars," and significantly impacts the pharmaceutical and medical device industries. The PPACA includes, among other things, the following measures:

- annual, non-deductible fees on any entity that manufactures or imports certain prescription drugs and biologics;
- increased Medicaid rebates owed by manufacturers under the Medicaid Drug Rebate Program for both branded and generic drugs;
- a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in and conduct comparative clinical research;
- new requirements for manufacturers to discount drug prices to eligible patients by 50% at the pharmacy level and for mail order services in order for their outpatient drugs to be covered under Medicare Part D;
- an increase in the number of entities eligible for discounts under the Public Health Service pharmaceutical pricing program; and
- establishes a licensure framework for follow-on biologic products.

The PPACA provisions on comparative clinical effectiveness research extend the initiatives of the American Recovery and Reinvestment Act of 2009, also known as the stimulus package, which included $1.1 billion in funding to study the comparative effectiveness of healthcare treatments and strategies. This stimulus funding was designated for, among other things, conducting, supporting or synthesizing research that compares and evaluates the risks and benefits, clinical outcomes, effectiveness and appropriateness of products. The PPACA also appropriates additional funding to comparative clinical effectiveness research. Although Congress has indicated

that this funding is intended to improve the quality of healthcare, it remains unclear how the research will impact current Medicare coverage and reimbursement or how new information will influence other third-party payor policies.

In addition, the PPACA provides for a prevention and health promotion outreach and education campaign to raise public awareness of health improvement, including obesity reduction and obesity-related services that are available to Medicaid enrollees. The PPACA also provides funding for projects designed to reduce childhood obesity.

We cannot predict what effect the PPACA or other healthcare reform initiatives that may be adopted in the future will have on our business. The continuing efforts of the government, insurance companies, managed care organizations and other payors of health care services to contain or reduce costs of health care may adversely affect:

- our and our current and any future collaborative partner's ability to set a price we believe is fair for our product candidates, if approved;
- our any our current or any future collaborative partner's ability to generate revenues and achieve or maintain profitability; and
- the availability of capital.

Our failure to successfully acquire, develop and market additional product candidates or approved products would impair our ability to grow.

As part of our corporate strategy, we may acquire, in-license, develop and/or market additional products and product candidates. Because our internal research capabilities are limited, we may be dependent upon pharmaceutical and biotechnology companies, academic scientists and other researchers to sell or license products or technology to us. The success of this strategy depends partly upon our ability to identify, select and acquire promising pharmaceutical product candidates and products.

The process of proposing, negotiating and implementing a license or acquisition of a product candidate or approved product is lengthy and complex. Other companies, including some with substantially greater financial, marketing and sales resources, may compete with us for the license or acquisition of product candidates and approved products. We have limited resources to identify and execute the acquisition or in-licensing of third-party products, businesses and technologies and integrate them into our current infrastructure. Moreover, we may devote resources to potential acquisitions or in-licensing opportunities that are never completed, or we may fail to realize the anticipated benefits of such efforts. We may not be able to acquire the rights to additional product candidates on terms that we find acceptable, or at all.

In addition, future acquisitions may entail numerous operational and financial risks, including:

- exposure to unknown liabilities;
- disruption of our business and diversion of our management's time and attention to develop acquired products or technologies;
- incurrence of substantial debt or dilutive issuances of securities to pay for acquisitions;
- higher than expected acquisition and integration costs;
- increased amortization expenses;
- difficulty and cost in combining the operations and personnel of any acquired businesses with our operations and personnel;
- impairment of relationships with key suppliers or customers of any acquired businesses due to changes in management and ownership; and
- inability to retain key employees of any acquired businesses.

Further, any product candidate that we acquire may require additional development efforts prior to commercial sale, including extensive clinical testing and approval by the FDA and applicable foreign regulatory authorities. All product candidates are prone to risks of failure typical of pharmaceutical product development, including the possibility that a product candidate will not be shown to be sufficiently safe and effective for approval by regulatory authorities. In addition, we cannot provide assurance that any products that we develop or approved products that we may acquire will be commercialized profitably or achieve market acceptance.

We may not be able to manage our business effectively if we are unable to attract and retain key personnel.

We may not be able to attract or retain qualified management and scientific and clinical personnel in the future due to the intense competition for qualified personnel among biotechnology, pharmaceutical and other businesses, particularly in the San Diego, California area. Our retention efforts may be particularly challenging in light of our historical regulatory interactions with our Contrave NDA and our workforce reductions completed in February and June 2011. Our industry has experienced a high rate of turnover of management personnel in recent years. If we are not able to attract, retain and motivate necessary personnel to accomplish our business objectives, we may experience constraints that will significantly impede the successful development and commercialization of our product candidates, our ability to raise additional capital and our ability to implement our overall business strategy.

We are highly dependent on the development, regulatory, commercial and financial expertise of our senior management, particularly Michael A. Narachi, our President and Chief Executive Officer. Although we have employment agreements with each of our executive officers, these agreements are terminable at will at any time with or without notice and, therefore, we may not be able to retain their services as expected. If we lose any members of our senior management team, including Mr. Narachi, we may not be able to find suitable replacements, and our business may be harmed as a result. We are not aware of any key personnel who has plans to retire or leave our company in the near future. In addition to the competition for personnel, the San Diego area in particular is characterized by a high cost of living. As such, we could have difficulty attracting experienced personnel to our company and may be required to expend significant financial resources in our employee recruitment and retention efforts.

In addition, we have scientific and clinical advisors who assist us in formulating our product development and clinical and regulatory strategies. These advisors are not our employees and may have commitments to, or consulting or advisory contracts with, other entities that may limit their availability to us, or may have arrangements with other companies to assist in the development of products that may compete with ours.

We will need to obtain FDA approval of our proposed product names, Contrave and Empatic, and any failure or delay associated with such approval may adversely impact our business.

Any name we intend to use for our product candidates will require approval from the FDA regardless of whether we have secured a formal trademark registration from the U.S. Patent and Trademark Office, or PTO. The FDA typically conducts a rigorous review of proposed product names, including an evaluation of potential for confusion with other product names. The FDA may also object to a product name if it believes the name inappropriately implies medical claims. If the FDA objects to the product names Contrave or Empatic, we may be required to adopt an alternative name for our initial product candidates. If we adopt an alternative name, we would lose the benefit of our existing trademark applications for Contrave and/or Empatic and may be required to expend significant additional resources in an effort to identify a suitable product name that would qualify under applicable trademark laws, not infringe the existing rights of third parties and be acceptable to the FDA. We and our current and any future collaborative partner may be unable to build a successful brand identity for a new trademark in a timely manner or at all, which would limit our and such collaborative partner's ability to commercialize our product candidates.

If we fail to comply with healthcare regulations, we could face substantial penalties and our business, operations and financial condition could be adversely affected.

As a manufacturer of pharmaceuticals, even though we do not and will not control referrals of healthcare services or bill directly to Medicare, Medicaid or other third-party payors, certain federal and state healthcare laws and regulations pertaining to fraud and abuse and patients' rights are and will be applicable to our business. We could be subject to healthcare fraud and abuse and patient privacy regulation by both the federal government and the states in which we conduct our business, without limitation. The laws that may affect our ability to operate include:

- the federal healthcare program Anti-Kickback Statute (as amended by the PPACA, which modified the intent requirement of the Anti-Kickback Statute so that a person or entity no longer needs to have actual knowledge of the statute or specific intent to violate it), which prohibits, among other things, persons from soliciting, receiving or providing remuneration, directly or indirectly, to induce either the referral of an individual, for an item or service or the purchasing or ordering of a good or service, for which payment may be made under federal healthcare programs such as the Medicare and Medicaid programs;
- federal false claims laws which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, claims for payment from Medicare, Medicaid, or other third-party payors that are false or fraudulent, and which may apply to entities like us which promote pharmaceutical products and provide coding and billing advice to customers, and under the PPACA, the government may assert that a claim including items or services resulting from a violation of the federal Anti-Kickback Statute constitutes a false or fraudulent claim for purposes of the federal false claims laws;
- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which prohibits executing a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters and which also imposes certain requirements relating to the privacy, security and transmission of individually identifiable health information;
- the Federal Food, Drug, and Cosmetic Act, which among other things, strictly regulates drug product marketing, prohibits manufacturers from marketing drug products for off-label use and regulates the distribution of drug samples; and
- state law equivalents of each of the above federal laws, such as anti-kickback and false claims laws which may apply to items or services reimbursed by any third-party payor, including commercial insurers, and state laws governing the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and often are not preempted by HIPAA, thus complicating compliance efforts.

Additionally, the compliance environment is changing, with more states, such as California and Massachusetts, mandating implementation of compliance programs, compliance with industry ethics codes, and spending limits, and other states, such as Vermont and Minnesota requiring reporting to state governments of gifts, compensation, and other remuneration to physicians. The PPACA also imposes new reporting and disclosure requirements on device and drug manufacturers for any "transfer of value" made or distributed to prescribers and other healthcare providers. Such information will be made publicly available in a searchable format. In addition, device and drug manufacturers will also be required to report and disclose any investment interests held by physicians and their immediate family members during the preceding calendar year. Although the statute required reporting by March 31, 2013 of payments and other transfers of value made in calendar year 2012, the CMS issued a final rule that will go into effect in April 2013 and require manufacturers to begin collecting required information on August 1, 2013, with the first reports due March 31, 2014. Failure to submit required information may result in civil monetary penalties of up to an aggregate of $150,000 per year (and up to an aggregate of $1 million per year for "knowing failures"), for all payments, transfers of value or ownership or investment interests not reported in an annual submission. Finally, under the PPACA, effective April 1, 2012,

pharmaceutical manufacturers and distributors must provide the U.S. Department of Health and Human Services with an annual report on the drug samples they provide to physicians. The shifting regulatory environment, along with the requirement to comply with multiple jurisdictions with different compliance and/or reporting requirements, increases the possibility that a pharmaceutical company may run afoul of one or more laws.

If our operations are found to be in violation of any of the laws described above or any other governmental regulations that apply to us, we may be subject to penalties, including civil and criminal penalties, damages, fines and the curtailment or restructuring of our operations. Any penalties, damages, fines, curtailment or restructuring of our operations could adversely affect our ability to operate our business and our financial results. Although compliance programs can mitigate the risk of investigation and prosecution for violations of these laws, the risks cannot be entirely eliminated. Any action against us for violation of these laws, even if we successfully defend against it, could cause us to incur significant legal expenses and divert our management's attention from the operation of our business. Moreover, achieving and sustaining compliance with applicable federal and state privacy, security and fraud laws may prove costly.

Our business involves the use of hazardous materials and we and our third-party manufacturers must comply with environmental laws and regulations, which can be expensive and restrict how we do business.

Our third-party manufacturers' activities involve the controlled storage, use and disposal of hazardous materials owned by us, including the components of our product candidates and other hazardous compounds. We and our manufacturers are subject to federal, state and local laws and regulations governing the use, manufacture, storage, handling and disposal of these hazardous materials. Although we believe that the safety procedures utilized by our third-party manufacturers for handling and disposing of these materials comply with the standards prescribed by these laws and regulations, we cannot eliminate the risk of accidental contamination or injury from these materials. In the event of an accident, state or federal authorities may curtail the use of these materials and interrupt our business operations. We do not currently maintain hazardous materials insurance coverage. If we are subject to any liability as a result of our third-party manufacturers' activities involving hazardous materials, our business and financial condition may be adversely affected.

Our business and operations would suffer in the event of system failures.

Despite the implementation of security measures, our internal computer systems and those of our 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 drug development programs. For example, the loss of clinical trial data from completed or ongoing clinical trials for Contrave or Empatic, including the Light Study, 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 were to result in a loss of or damage to our data or applications, or inappropriate disclosure of confidential or proprietary information, we could incur liability and the further development of our product candidates could be delayed.

Risks Related to Intellectual Property

Our market opportunity for Contrave and Empatic may be limited by the relatively small number of issued U.S. patents and foreign patents that we own or in-license. In addition, although we have additional U.S. and international patent applications pending which seek further protection of our product candidates, these applications may not issue on a timely basis or at all.

Contrave is currently protected, in part, by U.S. patent number 5,512,593 issued in April 1996 and U.S. patent number 5,817,665 issued in October 1998, which we have licensed on an exclusive basis from Dr. Lee Dante and which we collectively refer to as the Dante patents. Provided maintenance fees are paid, U.S. patent

number 5,512,593 is expected to expire in April 2013 and U.S. patent number 5,817,665 is expected to expire in March 2013. The Dante patents do not protect Contrave outside of the United States. The Dante patents cover compositions of certain specified opioid antagonists (including naltrexone) combined with certain specified antidepressants (including bupropion), and thus provide coverage for Contrave.

In addition to the Dante patents, Contrave is also currently protected by U.S. patent number 7,375,111, which we refer to as the Weber/Cowley composition patent, and U.S. patent number 7,462,626, which we refer to as the Weber/Cowley methods patent. Provided maintenance fees are paid, the Weber/Cowley composition patent is expected to expire in March 2025, and the Weber/Cowley methods patent is expected to expire in July 2024. Collectively, we refer to the Weber/Cowley composition patent and the Weber/Cowley methods patent as the Weber/Cowley patents. We own the Weber/Cowley patents, but they are subject to our license agreement with Oregon Health & Science University, or OHSU, and our license agreement with Duke University, or Duke. The Weber/Cowley patents cover the current composition of Contrave and methods of administering it to treat obesity. We and/or our licensors have filed a number of international counterparts to the Weber/Cowley patents in foreign countries. A European counterpart application to the Weber/Cowley patent has issued in the European Patent Office, or EPO, and provides protection for Contrave in the various EPO countries in which the patent has been registered. Several international counterparts to the Weber/Cowley patents have also issued in other foreign jurisdictions. However, we cannot provide assurance that other pending international counterparts will issue on a timely basis or at all. There is also no assurance that the currently pending claims in those foreign countries will not be rejected, that any such rejections and any future rejections will ultimately be overcome, nor that any claims that may issue will be sufficiently broad to protect Contrave in those foreign countries. Furthermore, we cannot be certain that the scope of any issued foreign patent will be consistent with the currently pending claims, as there is a significant likelihood that the scope of the currently pending claims will be modified. If a competitor is willing to challenge the scope or validity of the Dante patents and/or the Weber/Cowley patents, the competitor could file an NDA seeking approval any time before we obtain approval from the FDA of an NDA for Contrave and three years after we obtain such approval.

We have also filed patent applications, directed to various treatment and formulation aspects of Contrave, in the United States and certain foreign countries under the Patent Cooperation Treaty, or PCT. The PCT is an international treaty providing a unified procedure under which the initial filing of a single patent application can provide an effective filing date in each participating country in which appropriate steps are subsequently taken. Such steps have been taken in various foreign countries, including Europe and Japan, with respect to a number of our PCT filings. Thus, we now have patent applications pending in those foreign countries, along with our previous filings in the United States and certain non-PCT countries. These filings seek to provide further protection for Contrave in the United States and overseas, but we cannot provide assurance that the claims in these patent applications will issue in their current form or at all.

Our intellectual property protection for Empatic derives from U.S. patent number 7,109,198, which was issued in September 2006 and which we refer to as the Gadde patent, and from U.S. patent number 7,425,571, which was issued in September 2008. We have in-licensed these patents on an exclusive basis from Duke together with several related patent applications. The Gadde patent provides composition coverage for the Empatic zonisamide/bupropion combination and also covers methods for using Empatic to treat obesity and to reduce the risk of hypertension, diabetes or dyslipidemia. Provided maintenance fees are paid, the Gadde patent is also expected to expire in 2023. U.S. patent number 7,425,571 covers methods of using zonisamide (including combinations with bupropion) to cause weight loss. Provided maintenance fees are paid, this patent is expected to expire in 2023. U.S. patent number 7,754,748, which issued in July 2010, protects the use of zonisamide SR for reducing weight in overweight and obese subjects, and is expected to expire in 2023, provided maintenance fees are paid. In addition, Duke has filed international counterparts to the Gadde patent that have issued in several countries and are currently pending in others; however, there is no assurance that the claims in these applications will issue in their currently pending form or at all. We have also filed patent applications in the United States, under the PCT and in certain foreign countries with the goal of protecting the formulations and use of zonisamide SR, an ingredient in Empatic. The PCT filing has matured into patent applications in Europe and Japan. The

European application was allowed in early 2012. Thus we now have patent applications pending in the United States, Japan and certain other foreign countries. However, we cannot provide assurance that the claims in these patent applications will issue in their currently pending form or at all.

We may face additional competition outside of the United States as a result of a lack of patent enforcement in foreign countries and off-label use of other dosage forms of the generic components in our product candidates.

While we have filed patent applications in many countries outside the United States, and have obtained some patent coverage for certain of our product candidates in certain foreign countries, we do not currently have widespread patent protection for Contrave and Empatic outside the United States and have no protection in many foreign jurisdictions. Even if international patent applications ultimately issue or receive approval, it is likely that the scope of protection provided by such patents will be different from, and possibly less than, the scope provided by our corresponding U.S. patents. The success of our international market opportunity is dependent upon the enforcement of patent rights in various other countries. A number of countries in which we have filed or intend to file patent applications have a history of weak enforcement and/or compulsory licensing of intellectual property rights. Even if we have patents issued in these jurisdictions, there can be no assurance that our patent rights will be sufficient to prevent generic competition or unauthorized use.

We and our current and any future collaborative partner may face competition from the off-label use of other dosage forms of the generic components in our product candidates. In addition, others may attempt to commercialize our product candidate combinations in the countries of the European Union, Canada, Mexico, Japan or other markets, in some of which, we do not have patent protection for our product candidates. Due to the lack of patent protection for these combinations in some territories outside the United States and the potential for correspondingly lower prices for the drugs in those markets, it is possible that patients will seek to acquire the generic IR components of our product candidates (naltrexone IR and zonisamide IR), in those other territories. The off-label use of the generic IR components in the United States or the importation of the generic IR components from foreign markets could adversely affect the commercial potential for our product candidates and adversely affect our overall business and financial results.

We have in-licensed all or a portion of the rights to our product candidates from third parties. If we default on any of our material obligations under those licenses, we could lose rights to our product candidates.

We have in-licensed and otherwise contracted for rights to our product candidates, and we may enter into similar licenses in the future to supplement our product candidate pipeline. Under the relevant agreements, we are subject to commercialization, development, sublicensing, royalty, insurance and other obligations. If we or our current or any future collaborative partner fail to comply with any of these requirements, or otherwise breach these license agreements, the licensor may have the right to terminate the license in whole or to terminate the exclusive nature of the license. Loss of any of these licenses or the exclusive rights provided therein could harm our financial condition and operating results. For example, our license agreement with Dr. Dante requires us to use commercially reasonable efforts to develop, obtain regulatory approval of and commercialize Contrave. To the extent we are unable to comply with these obligations, the license may be terminated.

Restrictions on our patent rights relating to our product candidates may limit our and our current and any future collaborative partner's ability to prevent third parties from competing against us.

Our success will depend on our and our current and any future collaborative partner's ability to obtain and maintain patent protection for our product candidates, preserve our trade secrets, prevent third parties from infringing upon our proprietary rights and operate without infringing upon the proprietary rights of others. Composition of matter patents on APIs are generally considered to be the strongest form of intellectual property protection for pharmaceutical products as they apply without regard to any method of use. Entirely new individual chemical compounds, often referred to as new chemical entities, are typically entitled to composition

of matter coverage. Current law also allows novel and unobvious combinations of old compounds to receive composition of matter coverage for the combination. However, we cannot be certain that the current law will remain the same, or that our product candidates will be considered novel and unobvious by the PTO and courts.

In addition to composition of matter patents and patent applications, we also have issued and filed method of use patents and patent applications. This type of patent protects the use of the product only for the specified method. However, this type of patent does not prevent a competitor from making and marketing a product that is identical to our product for an indication that is outside the scope of the patented method. Moreover, even if these competitors do not actively promote their product for our targeted indication, physicians may prescribe these products "off-label." Although off-label prescriptions may infringe or contribute to the infringement of method of use patents, the practice is common and such infringement is difficult to prevent or prosecute.

Although we believe we and our licensors have conducted appropriate prior art searches relating to our key patents and patent applications, there is no assurance that all of the potentially relevant prior art has been found. Moreover, because the constituents of our combination product candidates have been on the market as separate monotherapeutic products for many years, it is possible that these monotherapies have previously been used off-label in such a manner that such prior usage would affect the validity of our method of use patents.

Patent applications in the United States and most other countries are confidential for a period of time until they are published, and publication of discoveries in scientific or patent literature typically lags actual discoveries by several months or more. As a result, we cannot be certain that we and the inventors of the issued patents and applications that we in-licensed were the first to conceive inventions covered by the patents and pending patent applications or that we and those inventors were the first to file patent applications for such inventions.

We and our current and any future collaborative partner also 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, some of whom assist with the development of other obesity drugs. We and our collaborative partner also have agreements with our employees and selected consultants that obligate them to assign their inventions to us. 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 that 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.

If we or our current or any future collaborative partner are sued for infringing intellectual property rights of third parties, it will be costly and time consuming, and an unfavorable outcome in that litigation would have a material adverse effect on our business.

Our commercial success depends upon our and our current and any future collaborative partner's ability to develop, manufacture, market and sell our product candidates and use our proprietary technologies without infringing the proprietary rights of third parties. Numerous U.S. and foreign issued patents and pending patent applications, which are owned by third parties, exist in the fields in which we and our collaborative partner are developing products. As the biotechnology and pharmaceutical industries expand and more patents are issued, the risk increases that our product candidates and/or proprietary technologies may give rise to claims of infringement of the patent rights of others. There may be issued patents of third parties of which we are currently unaware that may be infringed by our product candidates or proprietary technologies. Because patent applications can take many years to issue, there may be currently pending applications, unknown to us or our collaborative partner, which may later result in issued patents that our product candidates or proprietary technologies may infringe.

We may be exposed to, or threatened with, future litigation by third parties having patent or other intellectual property rights alleging that our product candidates and/or proprietary technologies infringe their

intellectual property rights. If one of these patents is found to cover our product candidates, proprietary technologies or their uses, we or our current or any future collaborative partner could be enjoined by a court and required to pay damages and could be unable to commercialize our product candidates or use our proprietary technologies unless we or they obtained a license to the patent. A license may not be available to us or our current or any future collaborative partner on acceptable terms, if at all. In addition, during litigation, the patent holder could obtain a preliminary injunction or other equitable relief which could prohibit us or our current or any future collaborative partner from making, using or selling our products, technologies or methods pending a trial on the merits, which could be years away.

There is a substantial amount of litigation involving patent and other intellectual property rights in the biotechnology and pharmaceutical industries generally. If a third party claims that we or our collaborative partner infringe its intellectual property rights, we may face a number of issues, including, but not limited to:

- infringement and other intellectual property claims which, regardless of merit, may be expensive and time-consuming to litigate and may divert our management's attention from our core business;
- substantial damages for infringement, which we may have to pay if a court decides that the product at issue infringes on or violates the third party's rights, and if the court finds that the infringement was willful, we could be ordered to pay treble damages and the patent owner's attorneys' fees;
- a court prohibiting us from selling or licensing the product unless the third party licenses its product rights to us, which it is not required to do;
- if a license is available from a third party, we may have to pay substantial royalties and fees and/or grant cross-licenses to intellectual property rights for our products; and
- redesigning our products or processes so they do not infringe, which may not be possible or may require substantial monetary expenditures and time.

We will be obtaining our bupropion SR, zonisamide SR, naltrexone SR, our finished Contrave and Empatic tablets combining these components, and the packaging for these tablets from third-party manufacturers. Each aspect of product design, formulation, manufacturing, packaging, and use has the potential to implicate third-party patent rights. We have taken various measures to reduce the potential for infringement. For example, we have in-licensed from GlaxoSmithKline certain formulation patents related to bupropion that expand our formulation options as we develop our commercial formulation of Contrave. However, we could be exposed to potential patent infringement liability from other third parties who hold patents on various formulations of bupropion and naltrexone.

No assurance can be given that patents do not exist, have not been filed, or could not be filed or issued, which contain claims covering these or other aspects of our products, technology or methods, as implemented by us or by third-party manufacturers with whom we contract. Because of the large number of patents issued and patent applications filed in our field, we believe there is a risk that third parties may allege they have patent rights encompassing our products, technology or methods. Such third-party patent rights, if relevant, could prevent us or our current or any future collaborative partner from adopting or marketing a particular formulation or product, or could expose us to patent infringement liability.

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.

Periodic maintenance fees on the Gadde patents covering Empatic and the Weber/Cowley patents covering Contrave, as well as our other issued patents, are due to be paid to the PTO in several stages over the lifetimes of the patents. We have systems in place to remind us to pay these fees, and we employ an outside firm, Computer Patent Annuities, to pay annuity fees due to foreign patent agencies on our issued and pending foreign patent applications. The PTO and various foreign governmental patent agencies require compliance with a number of

procedural, documentary, fee payment and other similar provisions during the patent application process. We employ reputable law firms and other professionals to help us comply, and in many cases, an inadvertent lapse can be cured by payment of a late fee or by other means in accordance with the applicable rules. However, there are situations in which noncompliance can result in abandonment or lapse of the patent or patent application, resulting in partial or complete loss of patent rights in the relevant jurisdiction. In such an event, our competitors might be able to enter the market and this circumstance would have a material adverse effect on our business.

We have not yet registered our trademarks in all of our potential markets, and failure to secure those registrations could adversely affect our business.

We have received U.S. trademark registration number 3396021 for our corporate logo for use in connection with pharmaceutical preparations and substances for the treatment of obesity, inducement of weight loss and prevention of weight gain. We have obtained trademark registrations in Canada, the European Union, and Japan for the same mark. In addition, we have received U.S. trademark registration number 3396807 for our corporate name OREXIGEN for use in connection with pharmaceutical preparations for the treatment of disorders of the central nervous system, or CNS, printed instructional, educational and teaching materials in the field of treatment and management of disorders of the CNS, and providing medical information in the field of disorders of the CNS. We have obtained trademark registrations in Canada, the European Union, and Japan for the same mark. We have obtained foreign trademark registrations for the corporate name Orexigen Therapeutics, Inc. in the European Union and Japan. We have received U.S. trademark registration number 3393576 for the mark CONTRAVE for use in connection with pharmaceutical preparations for use in the treatment of obesity and inducing weight loss. An intent-to-use application for the CONTRAVE mark has been allowed in the United States in connection with certain printed materials and medical information services. We have also obtained foreign trademark registrations for the mark CONTRAVE in Canada, Europe and Japan. In addition, applications for a Contrave logo for use in connection with pharmaceutical preparations for use in the treatment of obesity and inducing weight loss, certain printed materials and medical information services has been allowed in the U.S., and is pending in Canada. We also have a pending application for CONTRAVE in Canada which covers certain printed materials and medical information services. The Contrave logo is registered in Europe and Japan. An intent-to-use trademark application has been allowed in the United States for the mark EMPATIC for use in connection with pharmaceutical preparations for the treatment of obesity and inducing weight loss, various printed materials, and medical information services. Foreign trademark registrations have issued in the European Union and Japan for the mark EMPATIC, and an application remains pending in Canada. However, no assurance can be given that our allowed trademark applications will actually become registered, or that our registered trademarks can be maintained or enforced. During trademark registration proceedings in the various countries, we have received and expect to receive rejections. Although we are given an opportunity to respond to those rejections, there can be no assurance that the rejections can be successfully overcome. In addition, in the PTO and in many foreign jurisdictions, third parties are given an opportunity to oppose pending trademark applications and to cancel registered trademarks. For example, another pharmaceutical company opposed the registration of EXCALIA, the prior mark for the product candidate that we now call EMPATIC. No assurance can be given that opposition or cancellation proceedings will not be filed against our trademarks, nor can there be any assurance that our trademarks would survive such proceedings.

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

As is common in the biotechnology and pharmaceutical industries, we employ individuals who were previously employed at other biotechnology or pharmaceutical companies, including our competitors or potential competitors. Although no claims against us are currently pending, 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 their former employers. 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.

Risks Related to Our Finances and Capital Requirements

We have incurred significant operating losses since our inception and anticipate that we will incur continued losses for the foreseeable future.

We have focused primarily on developing our first two product candidates, Contrave and Empatic, with the goal of supporting regulatory approval for these product candidates. We have financed our operations almost exclusively through the sale of our preferred and common stock and debt and have incurred losses in each year since our inception in September 2002. As of December 31, 2012, we had an accumulated deficit of approximately $436.8 million. These losses, combined with expected future losses, have had and will continue to have an adverse effect on our stockholders' equity and working capital. We expect to continue to incur significant and increasing operating losses for the foreseeable future and such losses have had, and will continue to have, an adverse effect on our stockholders' equity. 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.

We have not generated any revenue from our product candidates and may never be profitable.

Our ability to become profitable depends upon our ability to generate revenue. With the exception of the $50 million upfront cash payment we received from Takeda upon execution of the collaboration agreement, we have not generated any revenue from our development-stage product candidates, and we do not know when, or if, we will generate any revenue. Our ability to generate revenue depends on a number of factors, including, but not limited to, our ability to:

- successfully complete future trials for Contrave and Empatic, including the Light Study and the Ignite Study;
- obtain regulatory approval for Contrave and Empatic;
- manufacture commercial quantities of our product candidates at acceptable cost levels if regulatory approvals are received;
- successfully manage our collaborative relationship with Takeda to effectively market and sell Contrave, if approved, in the United States, Canada and Mexico; and
- identify and enter into one or more additional strategic collaborations to effectively market and sell Empatic or market and sell Contrave outside the United States, Canada and Mexico, if approved.

Even if one or more of our product candidates is approved for commercial sale, which we do not expect to occur in the near future, we anticipate incurring significant costs associated with commercializing and continued development for any approved product. We may not achieve profitability soon after generating product sales, if ever. If we or our collaborative partner are unable to generate product revenues, we will not become sustainably profitable and may be unable to continue operations without continued funding.

We may need additional funds and/or need to enter into additional collaborative or other agreements in order to fund any additional clinical trials for Contrave beyond the Light Study, to the extent required, commercialize Contrave outside the United States, Canada and Mexico and continue the development of Empatic, and we may be unable to raise capital when needed or enter into such an agreement, which would force us to delay, reduce or eliminate any additional development activities required for Contrave, our commercialization efforts for Contrave outside such countries and our development efforts for Empatic.

Developing products for the obesity market, conducting clinical trials, establishing outsourced manufacturing relationships and successfully manufacturing and marketing drugs that we may develop is expensive. We believe that our existing cash, cash equivalents and short-term investments will be sufficient to meet our projected operating requirements through at least the next 12 months, including any required funds

needed to conduct the Light Study through the interim analysis and the Ignite Study. However, we have based these estimates on assumptions that may prove to be wrong, and we could spend our available financial resources much faster than we currently expect. Further, we will need additional capital to:

- fund the Light Study through the interim analysis in the event it takes longer to conduct to reach the interim analysis or costs more than anticipated;
- fund the Ignite Study in the event it takes longer to conduct or costs more than anticipated;
- fund our operations and continue to conduct clinical trials to support potential regulatory approval of Empatic;
- commercialize Contrave outside the United States, Canada and Mexico, Empatic or any other product candidates that we may develop, in-license or acquire, if any of these product candidates receives regulatory approval;
- co-promote Contrave in the United States, if it receives regulatory approval; and
- qualify and outsource the commercial-scale of our products under cGMP.

The amount and timing of our future funding requirements will depend on many factors, including, but not limited to:

- the rate of progress and cost of the Light Study, and the scope and cost of any additional clinical trials required for Contrave and clinical trials for Empatic, including expenses to support the trials and milestone payments that may become payable, and the decisions we make with respect to the continued development of such product candidates;
- the terms and timing of any collaborative, licensing, co-promotion or other arrangements that we may establish with respect to Contrave or Empatic;
- the costs of establishing sales, marketing and distribution capabilities in order to commercialize Contrave if and when it is approved for marketing, should we elect to do so;
- the costs involved in enforcing or defending patent claims or other intellectual property rights;
- the costs and timing of regulatory approvals for Contrave and Empatic, if at all;
- the extent to which we in-license, acquire or invest in other indications, products, technologies and businesses; and
- the successful commercialization of our products, if approved.

Future capital requirements will also depend on the extent to which we acquire or invest in additional complementary businesses, products and technologies. We currently have no commitments or agreements relating to any of these types of transactions.

Until we can generate a sufficient amount of product revenue and achieve profitability, we expect to finance future cash needs through public or private equity offerings, debt, receivables or royalty financings, or corporate collaboration and licensing arrangements, as well as through interest income earned on cash and investment balances. We cannot be certain that additional funding will be available on acceptable terms, or at all. If adequate funds are not available, we may be required to delay, reduce the scope of or eliminate one or more of our development programs or our commercialization efforts.

Our quarterly operating results may fluctuate significantly.

We expect our operating results to be subject to quarterly fluctuations. Our net loss and other operating results will be affected by numerous factors, including:

- variations in the level of expenses related to our two existing product candidates, including the conduct of the Light Study and the Ignite Study, or future development programs;

- regulatory developments affecting our product candidates or those of our competitors;
- the timing of future payments, if any, we may receive under our collaboration agreement with Takeda;
- our execution of any additional collaborative, licensing or similar arrangements, and the timing of payments we may make or receive under these arrangements;
- addition or termination of clinical trials, including the Light Study and the Ignite Study, or funding support;
- any intellectual property infringement lawsuit in which we may become involved; and
- if any of our product candidates receives regulatory approval, the level of underlying demand for our product candidates, wholesalers' buying patterns and with respect to Contrave, Takeda's performance under our collaboration agreement.

If our quarterly operating results fall below the expectations of investors or securities analysts, the price of our common stock could decline substantially. Furthermore, any quarterly fluctuations in our operating results may, in turn, cause the price of our stock to fluctuate substantially. We believe that quarterly comparisons of our financial results are not necessarily meaningful and should not be relied upon as an indication of our future performance.

Raising additional funds by issuing securities may cause dilution to existing stockholders and raising funds through lending and licensing arrangements may restrict our operations or require us to relinquish proprietary rights.

To the extent that we raise additional capital by issuing equity securities, our existing stockholders' ownership will be diluted. Debt, receivables and royalty financings typically contain covenants that restrict operating activities and may impair our ability to in-license potential products and/or product candidates. Debt, receivables and royalty financings may also be coupled with an equity component, such as warrants to purchase stock, which could also result in dilution of our existing stockholders' ownership.

If we raise additional funds through collaboration, licensing or other similar arrangements, it may be necessary to relinquish potentially valuable rights to our current product candidates, potential products or proprietary technologies, or grant licenses on terms that are not favorable to us. If adequate funds are not available, our ability to achieve profitability or to respond to competitive pressures would be significantly limited and we may be required to delay, significantly curtail or eliminate the development of one or more of our product candidates.

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

As a public company, we incur significant legal, accounting and other expenses. In addition, the Sarbanes-Oxley Act of 2002, or the Sarbanes-Oxley Act, as well as rules subsequently implemented by the Securities and Exchange Commission, or the SEC, and the Nasdaq Stock Market, Inc., or Nasdaq, have imposed various requirements on public companies, including establishment and maintenance of effective disclosure and financial controls and changes in corporate governance practices. Our management and other personnel devote a substantial amount of time to these compliance initiatives. Moreover, these rules and regulations result in increased legal and financial compliance costs and will make some activities more time-consuming and costly.

The Sarbanes-Oxley Act requires, among other things, that we maintain effective internal controls for financial reporting and disclosure. In particular, we are required to perform system and process evaluation and testing of our internal controls over financial reporting to allow management and our independent registered public accounting firm to report on the effectiveness of our internal controls over financial reporting, as required by Section 404 of the Sarbanes-Oxley Act. Our testing, or the subsequent testing by our independent registered

public accounting firm, may reveal deficiencies in our internal controls over financial reporting that are deemed to be material weaknesses. We have incurred and continue to expect to incur significant expense and devote substantial management effort toward ensuring compliance with Section 404. We currently do not have an internal audit function, and we may need to hire additional accounting and financial staff with appropriate experience and technical accounting knowledge. Moreover, if we do not comply with the requirements of Section 404, or if we or our independent registered public accounting firm identifies deficiencies in our internal controls that are deemed to be material weaknesses, the market price of our stock could decline and we could be subject to sanctions or investigations by Nasdaq, the SEC or other regulatory authorities, which would entail expenditure of additional financial and management resources.

Our results of operations and liquidity needs could be materially negatively affected by market fluctuations and economic downturn.

Our results of operations could be materially negatively affected by economic conditions generally, both in the U.S. and elsewhere around the world. Domestic and international equity markets have experienced and may continue to experience heightened volatility and turmoil based on domestic and international economic conditions and concerns. In the event these economic conditions and concerns continue and the markets continue to remain volatile, our results of operations could be adversely affected by those factors in many ways, including making it more difficult for us to raise funds if necessary, and our stock price may further decline. In addition, we maintain significant amounts of cash and cash equivalents at one or more financial institutions that are not federally insured. If economic instability continues, we cannot provide assurance that we will not experience losses on these investments.

We may lose the ability to use our net operating loss carryforwards, which could prevent or delay us from offsetting future taxable income.

We have incurred substantial losses during our history and do not expect to become profitable in 2013 and may never achieve profitability. To the extent that we continue to generate taxable losses, unused losses will carry forward to offset future taxable income, if any, until such unused losses expire. Our federal and state net operating loss carryforwards begin to expire in 2024 and 2015, respectively. Additionally, the future utilization of our net operating loss carryforwards to offset future taxable income is subject to annual limitations, pursuant to Sections 382 and 383 of the Internal Revenue Code of 1986, as amended, as a result of ownership changes that have occurred in prior years or may occur in the future, which could defer our ability to utilize or prevent us from fully utilizing our net operating loss carryforwards, which could have an adverse effect on our results of operations. Although we have determined that more likely than not an ownership change occurred in December 2012, we have not completed an update of our Section 382 analysis subsequent to December 31, 2010. When this analysis is finalized, we will reassess the amount of net operating losses and credits subject to limitation under Section 382.

Risks Relating to Securities Markets and Investment in Our Stock

The market price of our common stock has fluctuated and is likely to continue to fluctuate, which could reduce the market price of our common stock.

The market prices for securities of biotechnology and pharmaceutical companies have historically been highly volatile, and the market has from time to time experienced significant price and volume fluctuations that are unrelated to the operating performance of particular companies. Over the last several years, the overall capital markets have been highly volatile. Since the commencement of trading in connection with our initial public offering, or IPO, the publicly traded shares of our common stock have themselves experienced significant price and volume fluctuations. During the quarter ended December 31, 2012, the price per share for our common stock on the Nasdaq Global Market has ranged from a low sale price of $3.91 to a high sale price of $6.49. This market

volatility is likely to continue and could reduce the market price of our common stock, regardless of our operating performance. In addition, the trading price of our common stock could change significantly over short periods of time in response to many factors, including:

- FDA or international regulatory actions, including announcements concerning our NDA or our communications with the FDA for Contrave, including the timing of resubmission of the NDA, or failure to receive regulatory approval for any of our product candidates;
- announcements regarding our clinical trials, including the Light Study and the Ignite Study;
- announcements regarding Vivus' approved obesity product, including sales, safety and efficacy results, and its regulatory submissions and/or the results of its clinical trials;
- announcements regarding Arena's and Eisai's approved obesity product, including sales, safety and efficacy results once launched, and their regulatory submissions and/or the results of their clinical trials;
- announcements regarding our other competitors' regulatory submissions and/or the results of their clinical trials;
- announcements regarding our collaborative relationship with Takeda;
- announcements regarding bupropion, naltrexone or zonisamide;
- announcements regarding manufacturing or supply developments for Contrave or Empatic;
- failure of any of our product candidates, if approved, to achieve commercial success;
- developments concerning current or future strategic collaborations;
- announcements of the introduction of new products by us or our competitors;
- market conditions in the pharmaceutical and biotechnology sectors;
- announcements concerning product development results or intellectual property rights of others;
- litigation or public concern about the safety of our potential products;
- actual and anticipated fluctuations in our quarterly operating results;
- deviations in our operating results from the estimates of securities analysts or other analyst comments;
- additions or departures of key personnel;
- healthcare reform measures and other third-party coverage and reimbursement policies; and
- discussion of us or our stock price by the financial and scientific press and in online investor communities.

The realization of any of the risks described in these "Risk Factors" could also have a dramatic and material adverse impact on the market price of our common stock.

Future sales of our common stock may depress our stock price.

Any future sales of a substantial number of shares of our common stock in the public market such as that offering, or the perception that such sales may occur, could adversely affect the price of our common stock. We cannot predict the effect, if any, that market sales of those shares of common stock or the availability of those shares of common stock for sale will have on the market price of our common stock.

In addition, persons who were our stockholders prior to the sale of shares in our IPO continue to hold a substantial number of shares of our common stock that they may be able to sell in the public market, subject to the limitations of Rule 144 of the Securities Act of 1933, as amended. Significant portions of these shares are

held by a small number of stockholders. Sales by our current stockholders of a substantial number of shares, or the expectation that such sales may occur, could significantly reduce the market price of our common stock. For example, certain of our executive officers have established selling plans under Rule 10b5-1 of the Securities Exchange Act of 1934, as amended, or the Exchange Act, for the purpose of effecting specified sales of our common stock over a specified period of time. Moreover, the holders of a substantial number of shares of common stock may have rights, subject to certain conditions, to require us to file registration statements to permit the resale of their shares in the public market or to include their shares in registration statements that we may file for ourselves or other stockholders.

We have also registered all common stock that we may issue under our employee benefits plans. As a result, these shares can be freely sold in the public market upon issuance, subject to restrictions under the securities laws. In addition, our directors and executive officers may in the future establish programmed selling plans under Rule 10b5-1 of the Exchange Act for the purpose of effecting sales of our common stock, in addition to the already established plans. If any of these events cause a large number of our shares to be sold in the public market, the sales could reduce the trading price of our common stock and impede our ability to raise future capital.

Our executive officers, directors, principal stockholders and their respective affiliates will exercise significant influence over stockholder voting matters in a manner that may not be in the best interests of all of our stockholders.

As of March 1, 2013, our executive officers, directors, holders of 5% or more of our capital stock and their respective affiliates together controlled approximately 36% of our outstanding common stock. As a result, these stockholders will collectively be able to significantly influence all matters requiring approval of our stockholders, including the election of directors and approval of significant corporate transactions. The concentration of ownership may delay, prevent or deter a change in control of our company even when such a change may be in the best interests of some stockholders, could deprive our stockholders of an opportunity to receive a premium for their common stock as part of a sale of our company or our assets and might affect the prevailing market price of our common stock.

Anti-takeover provisions under our charter documents and Delaware law could delay or prevent a change of control which could limit the market price of our common stock and may prevent or frustrate attempts by our stockholders to replace or remove our current management.

Our amended and restated certificate of incorporation and amended and restated bylaws contain provisions that could delay or prevent a change of control of our company or changes in our board of directors that our stockholders might consider favorable. Some of these provisions include:

- a board of directors divided into three classes serving staggered three-year terms, such that not all members of the board will be elected at one time;
- a prohibition on stockholder action through written consent;
- a requirement that special meetings of stockholders be called only by the chairman of the board of directors, the chief executive officer, the president or by a majority of the total number of authorized directors;
- advance notice requirements for stockholder proposals and nominations;
- a requirement of approval of not less than 66 2/3% of all outstanding shares of our capital stock entitled to vote to amend any bylaws by stockholder action, or to amend specific provisions of our certificate of incorporation; and
- the authority of the board of directors to issue preferred stock on terms determined by the board of directors without stockholder approval.

In addition, we are governed by the provisions of Section 203 of the Delaware General Corporate Law, which may prohibit certain business combinations with stockholders owning 15% or more of our outstanding voting stock. These and other provisions in our amended and restated certificate of incorporation, amended and restated bylaws and Delaware law could make it more difficult for stockholders or potential acquirers to obtain control of our board of directors or initiate actions that are opposed by the then-current board of directors, including to delay or impede a merger, tender offer or proxy contest involving our company. Any delay or prevention of a change of control transaction or changes in our board of directors could cause the market price of our common stock to decline.

We have never paid dividends on our capital stock, and because we do not anticipate paying any cash dividends in the foreseeable future, capital appreciation, if any, of our common stock will be your sole source of gain on an investment in our stock.

We have paid no cash dividends on any of our classes of capital stock to date and we currently intend to retain our future earnings, if any, to fund the development and growth of our business. We do not anticipate paying any cash dividends on our common stock in the foreseeable future. As a result, capital appreciation, if any, of our common stock will be your sole source of gain for the foreseeable future.

We may become involved in securities class action litigation that could divert management's attention and harm our business and could subject us to significant liabilities.

The stock markets have from time to time experienced significant price and volume fluctuations that have affected the market prices for the common stock of pharmaceutical companies. These broad market fluctuations may cause the market price of our common stock to decline. In the past, securities class action litigation has often been brought against a company following a decline in the market price of its securities. This risk is especially relevant for us because biotechnology and biopharmaceutical companies have experienced significant stock price volatility in recent years. We may become involved in this type of litigation in the future. Litigation often is expensive and diverts management's attention and resources, which could adversely affect our business.

It is possible that securities class action litigation may be brought against us following stock price declines related to the release of information regarding our Contrave NDA or clinical trial results, including the Light Study. Any adverse determination in such litigation could subject us to significant liabilities.

Item 1B. Unresolved Staff Comments.

None.

Item 2. Properties.

In December 2007, we entered into a lease agreement covering approximately 22,229 square feet of office space which we use as our corporate headquarters in La Jolla, California. In September 2008, we entered into an amendment to lease an additional 9,312 square feet bringing the total leased space to 31,541 square feet. In February 2012, we entered into a partial lease termination agreement to reduce the amount of leased office space at our corporate headquarters to a total of 22,229 square feet of leased space. In February 2013, we entered into an amendment to extend our lease to September 2017. We have no laboratory, research or manufacturing facilities. We believe that our current facilities are adequate for our needs for the immediate future and that, should it be needed, suitable additional space will be available to accommodate expansion of our operations on commercially reasonable terms.

Item 3. Legal Proceedings.

None.

Item 4. Mine Safety Disclosures.

Not applicable.

PART II

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

Market Information

Our common stock is traded on the Nasdaq Global Market under the symbol "OREX."

The following table sets forth the high and low sales price of our common stock, as reported by the Nasdaq Global Market for the period indicated.

	High	Low
Year Ended December 31, 2012:		
Fourth Quarter	$ 6.49	$3.91
Third Quarter	7.73	3.76
Second Quarter	6.55	3.10
First Quarter	5.14	1.63
Year Ended December 31, 2011:		
Fourth Quarter	$ 2.34	$1.45
Third Quarter	2.68	1.22
Second Quarter	3.52	1.50
First Quarter	10.08	2.47

On March 11, 2013, the last reported sale price of our common stock on the Nasdaq Global Market was $6.64. As of March 11, 2013, there were 36 holders of record of our common stock.

Dividend Policy

We have never declared or paid any cash dividends on our capital stock and we do not currently intend to pay any cash dividends on our common stock. We expect to retain future earnings, if any, to fund the development and growth of our business. Any future determination to pay dividends on our common stock will be at the discretion of our board of directors and will depend upon, among other factors, our results of operations, financial condition, capital requirements and contractual restrictions.

Equity Compensation Plan Information

The following table summarizes securities available under our equity compensation plans as of December 31, 2012.

Plan Category	Shares Issuable Upon Exercise of Outstanding Awards	Weighted Average Exercise Price	Number of Securities Available for Future Issuance
Equity compensation plans approved by security holders:	13,838,894	$ 2.29	5,117,479(1)
Equity compensation plans not approved by security holders:	—	N/A	2,500,000(2)
Total	13,838,894	$ 2.29	7,617,479

(1) Represents shares reserved for issuance under the 2004 Stock Plan and the 2007 Equity Incentive Award Plan, as amended, or the 2007 Plan. The 2007 Plan was adopted at the time of our initial public offering which coincided with our discontinuation of granting awards under the 2004 Stock Plan. Stock options under the 2007 Plan have an exercise price equal to the fair market value of the underlying common stock at

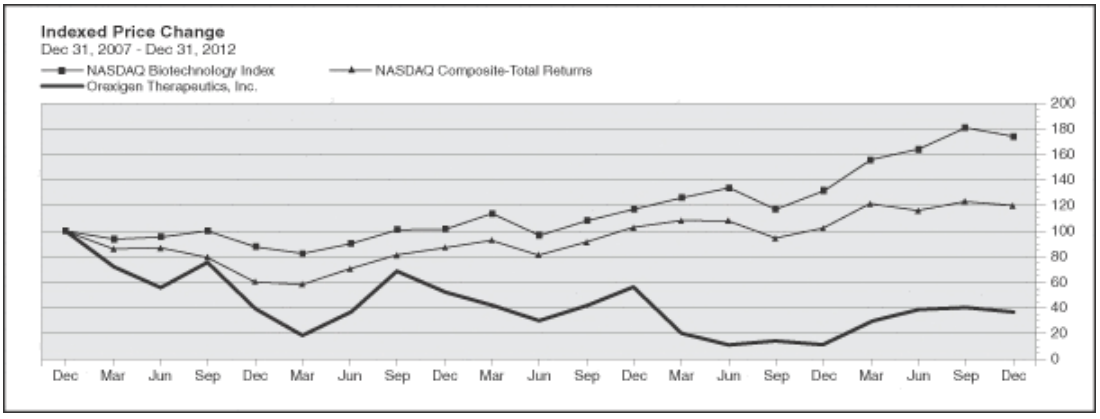
the date of grant, generally vest over a period of four years, and have a ten-year life. The 2007 Plan contains an "evergreen" provision which allows for annual increases in the number of shares available for future issuance on January 1 of each year during the ten-year term of the plan, beginning on January 1, 2008. The annual increase in the number of shares shall be equal to the lesser of (i) 15% of our outstanding common stock on the applicable January 1, (ii) 6,000,000 shares of common stock, or (iii) a lesser amount determined by our board of directors. The 2007 Plan provides that the maximum number of shares that may be granted pursuant to the exercise of incentive stock options granted under the plan is 40,000,000 shares.

(2) Represents shares reserved for issuance under the 2007 Plan to individuals not previously an employee or non-employee director of ours (or following a bona fide period of non-employment with us), as an inducement material to each individual's entering into employment with us, or the Inducement Reserve, within the meaning of Rule 5635(c)(4) of the NASDAQ Listing Rules, or Rule 5635(c)(4). The 2007 Plan was amended in October 2009 to provide for the reservation of 500,000 shares of our common stock to be issued pursuant to the Inducement Reserve without stockholder approval, as permitted under Rule 5635(c)(4). The 2007 Plan was further amended without stockholder approval in February 2010 to reserve an additional 2,000,000 shares of our common stock to be issued pursuant to the Inducement Reserve.

Comparative Stock Performance Graph

The information contained in this Stock Performance Graph section shall not be deemed to be "soliciting material" or "filed" with the SEC or subject to the liabilities of Section 18 of the Exchange Act unless we specifically incorporate it by reference into a document filed under the Securities Act or the Exchange Act.

The following graph illustrates a comparison of the total cumulative stockholder return on our common stock since April 26, 2007, which is the date our common stock first began trading on the Nasdaq Global Market, to two indices: the Nasdaq Composite Index and the Nasdaq Biotechnology Index. The graph assumes an initial investment of $100 on April 26, 2007. The comparisons in the graph are required by the Securities and Exchange Commission and are not intended to forecast or be indicative of possible future performance of our common stock.



	April 26, 2007	December 31, 2012
Orexigen Therapeutics, Inc.	$ 100	$ 37
Nasdaq Composite Index	$ 100	$ 120
Nasdaq Biotechnology Index	$ 100	$ 174

Sales of Unregistered Securities

None.

Repurchases of Equity Securities

None.

Item 6. Selected Financial Data

The following selected financial data should be read together with our financial statements and related notes, and "Management's Discussion and Analysis of Financial Condition and Results of Operations" included elsewhere in this annual report.

	Years Ended December 31,				
	2012	2011	2010	2009	2008
	(In thousands, except per share amounts)				
Statement of Operations Data:					
Revenues:					
Collaborative agreement	$ 3,428	$ 3,428	$ 1,143	$ —	$ —
License revenue	—	971	88	88	88
Total revenues	3,428	4,399	1,231	88	88
Operating expenses:					
Research and development	73,680	12,780	28,131	47,441	79,261
General and administrative	19,987	19,502	24,495	18,177	15,651
Total operating expenses	93,667	32,282	52,626	65,618	94,912
Loss from operations	(90,239)	(27,883)	(51,395)	(65,530)	(94,824)
Other income (expense):					
Interest income	147	46	124	333	3,115
Interest expense	(2)	(221)	(644)	(1,365)	(1,531)
Total other income (expense)	145	(175)	(520)	(1,032)	1,584
Net loss attributable to common stockholders	$ (90,094)	$ (28,058)	$ (51,915)	$ (66,562)	$ (93,240)
Basic and diluted net loss per share (1)	$ (1.27)	$ (0.58)	$ (1.10)	$ (1.67)	$ (2.76)
Shares used to calculate net loss per share (1)	70,739	48,273	47,377	39,905	33,762

(1) See Note 2 of Notes to Financial Statements for an explanation of the method used to calculate the net loss per share and the number of shares used in the computation of the per share amounts.

	As of December 31,				
	2012	2011	2010	2009	2008
	(In thousands)				
Balance Sheet Data:					
Cash and cash equivalents and investment securities, available-for-sale	$ 137,403	$ 147,593	$ 92,366	$ 92,158	$ 86,167
Working capital	113,780	141,013	78,580	77,387	60,862
Total assets	139,154	149,700	96,846	96,848	91,908
Long-term debt, less current portion	—	—	—	2,416	8,800
Accumulated deficit	(436,804)	(346,710)	(318,652)	(266,737)	(200,175)
Total stockholders' equity	75,469	99,706	33,788	75,903	53,794

Item 7. Management's Discussion And Analysis Of Financial Condition And Results Of Operations

The following discussion and analysis of our financial condition and results of operations should be read in conjunction with "Item 6—Selected Financial Data" and our financial statements and related notes appearing elsewhere in this annual report. In addition to historical information, this discussion and analysis contains forward-looking statements that involve risks, uncertainties and assumptions. Our actual results may differ materially from those anticipated in these forward-looking statements as a result of certain factors, including but not limited to those set forth under "Item 1A—Risk Factors" and elsewhere in this annual report.

Overview

Background

We are a biopharmaceutical company focused on the development of pharmaceutical product candidates for the treatment of obesity. Our product candidates are Contrave®, which has completed Phase III clinical trials and which is currently being studied in a cardiovascular outcomes trial, and Empatic™, which has completed Phase II clinical trials. Each of these product candidates is a combination of generic drug components, each of which has already received regulatory approval for other indications and been commercialized. We are developing these combinations in an effort to demonstrate adequate efficacy and safety for potential regulatory approval. We have not yet received regulatory approval for either product candidate.

In January 2011, we received a complete response letter, or CRL, from the U.S. Food and Drug Administration, or FDA, concerning our previously-submitted New Drug Application, or NDA, for Contrave. A CRL is issued by the FDA when the review of an NDA is completed and questions remain that precludes the approval of the NDA in its current form. The CRL for Contrave indicated that the FDA could not approve the NDA in its present form primarily due to concerns regarding the cardiovascular safety profile of Contrave when used long-term in a population of overweight and obese patients. The CRL stated that before our NDA could be approved, we must conduct a randomized, double-blind, placebo-controlled trial of sufficient size and duration to demonstrate that the risk of major adverse cardiovascular events, or MACE, in overweight and obese patients treated with Contrave does not adversely affect the drug's benefit-risk profile.

In September 2011, following a meeting with senior officials in the FDA's Office of New Drugs, or OND, we received written correspondence from the director of the OND detailing the OND's design requirements for a randomized, double-blind, placebo-controlled cardiovascular outcomes trial, or CVOT, for Contrave that would address the CRL. The CVOT is a randomized, double-blind, placebo-controlled cardiovascular outcomes trial evaluating the occurrence of MACE in patients participating in the study. Importantly, if the interim analysis excludes a doubling of risk of MACE in patients receiving Contrave compared to placebo, we plan to resubmit the Contrave NDA to the FDA for approval. The exclusion of a doubling of risk of MACE was established as the threshold for approvability of Contrave during discussions with the FDA prior to the start of the CVOT. An interim analysis is planned once the CVOT's independent Data Monitoring Committee has determined that sufficient information has been gathered for the analysis that would include at least 87 adjudicated MACE. In February 2012 we reached agreement with the FDA on a Special Protocol Assessment, or SPA, for the CVOT. An SPA is a written agreement with the FDA on the details of the design and planned analysis for a clinical trial. An SPA is generally binding upon the FDA unless a substantial scientific issue essential to determining safety or efficacy is identified after the trial begins.

In October, 2012, we announced that we received a response to a formal dispute resolution request from the FDA's Center for Drug Evaluation and Research, or CDER. We had requested that Contrave be considered for approval on the basis of existing data together with a postmarketing requirement to supply the interim analysis of the Light Study shortly after approval. CDER denied this request, reaffirming that the cardiovascular outcomes data from the interim analysis of the Light Study is required prior to approval; however, CDER indicated that it was highly supportive of the exploration of a faster path to resubmission of the Contrave NDA. In January 2013, the FDA's Division of Metabolism and Endocrinology Products, or DMEP, proposed a resubmission procedure that would allow the independent Data Monitoring Committee's summary report of the CVOT interim analysis to

form the basis of a resubmission of the Contrave NDA. The complete clinical study report, or CSR, for the interim analysis, which would ordinarily form the basis for the NDA resubmission filing, would be provided to the FDA during its review of the NDA within 60 days of the NDA resubmission.

We initiated the CVOT, which we refer to as the Light Study, in June 2012, and completed screening in December 2012 which resulted in approximately 8,900 patients randomized to treatment. We enrolled a patient population that we predicted would have an annualized MACE rate between 1% and 2%. The timing of the interim analysis and the Contrave NDA resubmission is dependent on the timing of MACE observed in the Light Study. The observed MACE rate may differ materially from modeled MACE rate. We are preparing to be ready to conduct the interim analysis and resubmit the Contrave NDA in 2013. However, if the observed MACE rate is at or near the low end of the targeted range of 1% to 2%, the resubmission of the Contrave NDA may not occur until early 2014.

In October 2012, we completed a public offering of 11,000,000 shares of our common stock at a public offering price of $5.50 per share. Net cash proceeds from the public offering were approximately $56.5 million, after deducting underwriting discounts and commissions and estimated offering expenses payable by us.

In December 2011, we completed a public offering of 5,646,173 units. Each unit consists of one share of common stock and a warrant to purchase ten shares of common stock, at a price to the public of $1.45 per share of common stock and $1.449 per warrant to purchase each share of common stock, which together comprise the purchase price of $15.94 per unit. Net cash proceeds from the public offering were $86.9 million, after deducting underwriting discounts and commissions and offering expenses. The warrants issued in the transaction have an exercise price equal to $0.001 per share. Each warrant is exercisable in whole or in part for a period of 10 years commencing on December 22, 2011, subject to certain limitations set forth in the warrant.

Our primary activities since incorporation have been organizational activities, including recruiting personnel, conducting research and development, including clinical trials, and raising capital. We have incurred significant net losses since our inception. As of December 31, 2012, we had an accumulated deficit of $436.8 million. These losses have resulted principally from costs incurred in connection with research and development activities, primarily costs of clinical trial activities associated with our current product candidates, and general and administrative expenses. We expect to continue to incur losses for the next several years. Successful transition to attaining profitable operations is dependent upon achieving a level of revenues adequate to support our cost structure, and until that time, we may need to continue to raise additional equity or debt financing.

Revenues

We generated approximately $3.4 million in revenue in 2012, resulting from the sublicensing of technology and amounts earned under our collaboration agreements. In September 2010, we entered into a collaboration agreement with Takeda Pharmaceutical Company Limited, or Takeda, to develop and commercialize Contrave in the United States, Canada and Mexico. Under the collaboration agreement, we received an upfront, nonrefundable cash payment of $50.0 million from Takeda and this amount is being recognized ratably over the estimated life of the agreement. For 2012, 2011 and 2010, we recognized revenue of $3.4 million, $3.4 million and $1.1 million, respectively, related to the Takeda agreement.

During 2005, we sublicensed technology to Cypress Bioscience, Inc., or Cypress, for an upfront payment of $1.5 million, and this amount was being recognized ratably over the estimated life of the sublicensed patent. In January 2011, Cypress exercised its right to terminate the agreement. The remaining deferred revenue of $971,000 was recognized in the first quarter ending March 31, 2011.

Other than the amortization of the upfront payment of $50.0 million from Takeda, we do not expect to generate any significant revenues from licensing, achievement of milestones or product sales unless and until we are able to obtain regulatory approval of, and commercialize, our product candidates.

Takeda accounted for 100%, 78% and 93% of revenue for the years ended December 31, 2012, 2011 and 2010, respectively. Cypress accounted for 0%, 22% and 7% of revenue for the years ended December 31, 2012, 2011 and 2010, respectively.

Research and Development Expenses

The majority of our operating expenses to date have been incurred in research and development activities. Our research and development expenses consisted primarily of costs associated with clinical trials managed by our contract research organizations, or CROs, product development efforts and manufacturing costs. License fees, salaries and related employee benefits for certain personnel, and costs associated with certain non-clinical activities such as regulatory expenses, are also included in this amount. Our most significant costs to date are expenses incurred in connection with the clinical trials for Contrave and Empatic. The clinical trial expenses included payments to vendors such as CROs, investigators, suppliers of clinical drug materials and related consultants. We charge all research and development expenses to operations as incurred because the underlying technology associated with these expenditures relates to our research and development efforts and has no alternative future uses.

Our internal research and development resources are not directly tied to any individual research project and are primarily deployed across our Contrave and Empatic programs, both of which target the obesity market. We are developing our two obesity product candidates in parallel and, due to the fact that we use shared resources across projects, we do not maintain information regarding our internal costs incurred for our research and development programs on a program-specific basis. We use external service providers to manage our clinical trials, to manufacture the product supplies used in these trials and for formulations development, consulting and other activities.

The following table summarizes our research and development expenses for the year ended December 31, 2012. Costs that are not attributable to a specific research program are included in the "Other" category (in thousands):

Costs of external service providers:	
Obesity	$65,554
Other	248
Subtotal	65,802
Internal costs	6,063
Stock-based compensation	1,815
Total research and development costs	$ 73,680

At this time, due to the risks inherent in the drug development process, we are unable to estimate with any certainty the costs we will incur in the continued development, if any, of our product candidates for potential commercialization. Specifically, we cannot quantify the development expenses associated with completion of the Light Study for Contrave or the development of Empatic. Prior to its commencement, we anticipated that the costs to conduct the Light Study to the interim analysis would be approximately $100.0 million. We believe the costs we have incurred to date and expect to incur in the future in connection with the conduct of the Light Study are consistent with our original projection. With respect to Empatic, prior to initiating Phase III studies, we plan to seek a collaboration partner to help fund Phase III clinical development of and, if approved, commercialization of this product candidate. However, we cannot forecast with any degree of certainty whether such a collaboration arrangement will be secured, if at all, and to what degree such arrangement would affect our development plans and capital requirements. As such, until we finalize any future development plans for Empatic, including based on additional feedback from the FDA and our ability to secure a collaboration partner, we are not able to estimate the expenses required to further develop Empatic. Future development expenses will depend on the scope and

timing of the Light Study and any other additional clinical trials for Contrave, if any, our financial resources, our ability to secure a collaboration partner for, as well as decisions made with respect to the development of, Empatic and ongoing assessments as to each product candidate's commercial potential. Clinical development timelines, the probability of success and development costs can differ materially from expectations. The lengthy process of completing our clinical trials, including the Light Study, and seeking regulatory approval for our product candidates requires the expenditure of substantial resources. Any failure by us or delay in completing our clinical trials, including the Light Study, or in obtaining regulatory approvals, could cause a delay in the commencement of product revenues and cause our research and development expenses to increase and, in turn, have a material adverse effect on our results of operations. We do not expect Contrave to be commercially available in any major market until 2014, if at all, and Empatic to be commercially available in any major market for at least several years, if at all.

General and Administrative

Our general and administrative expenses consist primarily of salaries and related costs for personnel in executive, finance, accounting and internal support functions. In addition, general and administrative expenses include professional fees for legal, consulting and accounting services. We anticipate general and administrative expenses to remain generally unchanged as we continue to pursue the development of Contrave and Empatic.

Other Income (Expense)

Other income consists of interest earned on our cash, cash equivalents and investment securities. Interest expense consists of interest incurred in connection with the $25.0 million credit and security agreement, as amended, with GE Healthcare Financial Services which was paid in full and terminated in July 2011.

Income Taxes

At December 31, 2012, we have federal and state net operating loss carryforwards of approximately $289.0 million and $266.0 million, respectively. The federal and state net operating loss carryforwards begin to expire in 2024 and 2015, respectively, unless previously utilized. At December 31, 2012, we have federal and state research and development tax credit carryforwards of $12.0 million and $3.9 million, respectively. The federal research and development tax credit carryforwards begin to expire in 2024 unless previously utilized and the state tax credits carry forward indefinitely. Under Section 382 and 383 of the Internal Revenue Code of 1986, as amended, or the Internal Revenue Code, substantial changes in our ownership may limit the amount of net operating loss carryforwards that could be utilized annually in the future to offset taxable income. Although we have determined that more likely than not an ownership change has occurred in December 2012, we have not completed an update of our Section 382 analysis subsequent to December 31, 2010. Until this analysis has been updated, we have removed deferred tax assets for net operating losses of $505.4 million and research and development credits of $9.6 million from our deferred tax asset schedule and have recorded a corresponding decrease to our valuation allowance. When this analysis is finalized, we will reassess the amount of net operating losses and credits subject to limitation under Section 382. Due to the existence of the valuation allowance, future changes in the deferred tax assets related to these tax attributes will not impact our effective tax rate.

Critical Accounting Policies and Estimates

Our management's discussion and analysis of our financial condition and results of operations is based on our financial statements, which have been prepared in conformity with generally accepted accounting principles in the United States. The preparation of these financial statements requires us to make estimates and assumptions that affect the reported amounts of assets, liabilities, expenses and related disclosures. Actual results could differ from those estimates.

We believe the following accounting policies to be critical to the judgments and estimates used in the preparation of our financial statements.

Research and Development Expenses

A substantial portion of our ongoing research and development activities are or are expected to be performed under agreements we enter into with external service providers, including CROs, which conduct many of our research and development activities. We accrue for costs incurred under these contracts based on factors such as estimates of work performed, patient enrollment, patient visits to clinical sites for routine testing associated with the clinical trials, and progress of clinical studies and other events. However, the level of estimates can be significant. To date, we have not made any material adjustments to our estimates of clinical trial expenses. We make good faith estimates that we believe to be accurate, but the actual costs and timing of clinical trials are highly uncertain, subject to risks and may change depending upon a number of factors, including our clinical development plan.

Revenue Recognition

We have a collaboration agreement with Takeda and prior to its termination in January 2011, had a license agreement with Cypress, which contain multiple elements, including nonrefundable upfront fees, payments for reimbursement of research costs, payments associated with achieving specific development milestones and royalties based on specified percentages of net product sales, if any.

Prior to the revised multiple element and milestone method of revenue recognition guidance adopted by us on January 1, 2011, nonrefundable, up-front license fees and milestone payments with standalone value that are not dependent on any future performance by us under the agreements were recognized as revenue upon the earlier of when payments are received or collection is assured, but were deferred if we had continuing performance obligations. If we had continuing involvement through contractual obligations under such agreements, such up-front fees were deferred and recognized over the period for which we continued to have a performance obligation. Both the Takeda and Cypress agreements had continuing obligations, and as a result the up-front fees were deferred upon receipt.

Effective January 1, 2011, for multiple element agreements entered into or materially modified after December 31, 2010, we follow the provisions of ASU No. 2009-13. During 2011, we did not enter into any new collaborations. In order to account for the multiple-element arrangements, we identify the deliverables included within the agreement and evaluate which deliverables represent separate units of accounting. Analyzing the arrangement to identify deliverables requires the use of judgment, and each deliverable may be an obligation to deliver services, a right or license to use an asset, or another performance obligation. A delivered item is considered a separate unit of accounting when the delivered item has value to the partner on a standalone basis based on the consideration of the relevant facts and circumstances for each arrangement. Factors considered in this determination include the research capabilities of the partner and the availability of research expertise in this field in the general marketplace. Arrangement consideration is allocated at the inception of the agreement to all identified units of accounting based on their relative selling price. The relative selling price for each deliverable is determined using vendor-specific objective evidence ("VSOE") of selling price or third-party evidence of selling price if VSOE does not exist. If neither VSOE nor third-party evidence of selling price exists, we use our best estimate of the selling price for the deliverable. The amount of allocable arrangement consideration is limited to amounts that are fixed or determinable. The consideration received is allocated among the separate units of accounting, and the applicable revenue recognition criteria are applied to each of the separate units. Changes in the allocation of the sales price between delivered and undelivered elements can impact revenue recognition but do not change the total revenue recognized under any agreement. Upfront license fee payments are recognized upon delivery of the license if facts and circumstances dictate that the license has standalone value from the undelivered items, which generally include research and development services and the manufacture of drug products, the relative selling price allocation of the license is equal to or exceeds the upfront

license fee, persuasive evidence of an arrangement exists, our price to the partner is fixed or determinable, and collectability is reasonably assured. The adoption of this new accounting standard did not have a material impact on our results of operations or financial position.

Upfront license fee payments are deferred if facts and circumstances dictate that the license does not have standalone value. The determination of the length of the period over which to defer revenue is subject to judgment and estimation and can have a material impact on the amount of revenue recognized in a given period.

The terms of our collaboration agreements provide for milestone payments upon achievement of certain regulatory/development and sales-based events. Effective January 1, 2011, we adopted on a prospective basis the guidance under ASU No. 2010-17, "Revenue Recognition-Milestone Method". Under the Milestone Method of accounting, we recognize consideration that is contingent upon the achievement of a milestone in its entirety as revenue in the period in which the milestone is achieved only if the milestone is substantive in its entirety. A milestone is considered substantive when it meets all of the following three criteria: 1) The consideration is commensurate with either the entity's performance to achieve the milestone or the enhancement of the value of the delivered item(s) as a result of a specific outcome resulting from the entity's performance to achieve the milestone, 2) The consideration relates solely to past performance, and 3) The consideration is reasonable relative to all of the deliverables and payment terms within the arrangement. A milestone is defined as an event (i) that can only be achieved based in whole or in part on either the entity's performance or on the occurrence of a specific outcome resulting from the entity's performance, (ii) for which there is substantive uncertainty at the date the arrangement is entered into that the event will be achieved and (iii) that would result in additional payments being due to us. The adoption of this new accounting standard did not have a material impact on our results of operations or financial position.

Royalties to be received based on sales of our licensed products by partners will be recognized as earned.

Stock-Based Compensation

We account for stock-based compensation to employees in accordance with the fair value method of accounting for stock-based compensation arrangements which requires us to expense the estimated fair value of non-cash, stock-based payments to employees. Share-based payment transactions with employees are recognized in the financial statements based on their fair value and recognized as compensation expense over the vesting period.

We grant options to purchase our common stock to our employees, directors and non-employees under our 2007 equity incentive award plan. Stock-based compensation expense for the years ended December 31, 2012, 2011 and 2010 was $7.6 million, $6.6 million and $8.3 million, respectively. At December 31, 2012, total unrecognized estimated stock-based compensation expense related to non-vested stock options granted prior to that date was $24.6 million, which is expected to be recognized over a weighted-average period of 2.7 years.

We calculate the fair value of stock option grants using the Black-Scholes option-pricing model. The determination of the fair value of stock-based payment awards on the date of grant using an option-pricing model is affected by our stock price as well as assumptions regarding a number of complex and subjective variables. These variables include, but are not limited to, our expected stock price volatility over the term of the awards, risk-free interest rate and the expected term of the awards.

The weighted average expected life of options was calculated using the simplified method as prescribed by the Securities Exchange Commission. This decision was based on the lack of relevant historical data due to our limited historical experience. For options granted during the year ended December 31, 2012, we have calculated a weighted average expected term of 6.0 years. In addition, due to our limited historical data, the estimated volatility incorporates the historical volatility of comparable companies whose share prices are publicly available. For purposes of estimating the fair value of stock options granted during 2012 using the Black-Scholes model, we used an estimated weighted average stock price volatility of 87.5%.

The risk-free interest rate assumption was based on the United States Treasury's rates for U.S. Treasury zero-coupon bonds with maturities similar to those of the expected term of the award being valued (weighted-average risk-free interest rate of 1.1% for the year ended December 31, 2012). The assumed dividend yield was based on our expectation of not paying dividends in the foreseeable future.

For 2012, 2011 and 2010, we have reduced stock-based compensation expense recognized in the Statement of Operations to reflect estimated forfeitures. Forfeitures are estimated at the time of grant and revised, if necessary, in subsequent periods if actual forfeitures differ from those estimates. Pre-vesting forfeitures were estimated to be approximately 10.0% for all years ended December 31, 2012, 2011 and 2010 based on historical experience.

Equity instruments issued to non-employees are recorded at their fair value and are periodically revalued as the equity instruments vest and are recognized as expense over the related service period.

Income Taxes

We follow the provisions of the Income Taxes Topic of the Financial Accounting Standards Board, or FASB, Accounting Standards Codification, that defines a recognition threshold and measurement attributes for financial statement recognition and measurement of a tax provision taken or expected to be taken in a tax return. The topic also provides guidance on de-recognition, classification, interest and penalties, accounting in interim periods, disclosure and transition. Under the topic, the impact of an uncertain income tax position on the income tax return must be recognized at the largest amount that is more-likely-than-not to be sustained upon audit by the relevant taxing authority. An uncertain income tax position will not be recognized if it has less than a 50% likelihood of being sustained.

Deferred tax assets and liabilities are determined based on the differences between the financial reporting and tax basis of assets and liabilities using enacted tax rates which will be in effect when the differences reverse. We provide a valuation allowance against net deferred tax assets unless, based upon the available evidence, it is more likely than not that the deferred tax asset will be realized.

Results of Operations

Comparison of year ended December 31, 2012 to year ended December 31, 2011

Revenues. Revenues for the years ended December 31, 2012 and 2011 were $3.4 million and $4.4 million, respectively. The decrease of approximately $1.0 million was due to the decrease in revenue recognized under the license agreement with Cypress of $971,000.

Research and Development Expenses. Research and development expenses increased to $73.7 million for the year ended December 31, 2012 from $12.8 million in 2011. This increase of approximately $60.9 million was due primarily to an increase in expenses in connection with the Contrave Light Study, related proprietary product formulation work and consulting activities of $61.9 million. The increase was partially offset by a decrease in salaries and personnel related costs of $1.9 million. Research and development expenses for 2011 included employee termination costs of $2.6 million as a result of our corporate realignment.

General and Administrative Expenses. General and administrative expenses increased to $20.0 million for the year ended December 31, 2012 from $19.5 million in 2011. This decrease of approximately $500,000 was due primarily to a decrease in salaries and personnel related costs of approximately $1.2 million. The decrease was partially offset by an increase in market research costs of $858,000. General and administrative expenses for 2011 included employee termination costs of $1.4 million as a result of our corporate realignment.

Interest Income. Interest income increased to $147,000 for the year ended December 31, 2012 from $46,000 in 2011. This increase of approximately $101,000 was primarily due to higher interest rates and an increase in investment balances as compared to 2011.

Interest Expense. Interest expense decreased to $2,000 for the year ended December 31, 2012 from $221,000 in 2011. This decrease of $219,000 was due to the debt under the credit and security agreement with GE Healthcare Financial Services being paid in full in July 2011.

Comparison of year ended December 31, 2011 to year ended December 31, 2010

Revenues. Revenues for the years ended December 31, 2011 and 2010 were $4.4 million and $1.2 million, respectively. The increase of approximately $3.1 million was due to the revenue recognized under the collaboration agreement with Takeda of $2.3 million and the increase in revenue recognized under the license agreement with Cypress of $883,000.

Research and Development Expenses. Research and development expenses decreased to $12.8 million for the year ended December 31, 2011 from $28.1 million in 2010. This decrease of approximately $15.3 million was due primarily to a decrease in costs incurred in connection with the preparation for our NDA filing and FDA Advisory Committee meeting for Contrave of $4.6 million, a decrease in salaries and personnel related costs totaling approximately $3.2 million, a decrease in license fees of $3.1 million, a decrease in expenses in connection with our Contrave Phase III clinical trials, related proprietary product formulation work and consulting activities totaling $2.8 million and a decrease in stock-based compensation expense of approximately $1.4 million.

General and Administrative Expenses. General and administrative expenses decreased to $19.5 million for the year ended December 31, 2011 from $24.5 million in 2010. This decrease of approximately $5.0 million was due primarily to a decrease in salaries and personnel related costs of approximately $1.6 million, a decrease in market research costs totaling $1.3 million, a decrease in medical affairs expense of $668,000 and a decrease in stock-based compensation expense of approximately $305,000.

Interest Income. Interest income decreased to $46,000 for the year ended December 31, 2011 from $124,000 in 2010. This decrease of approximately $78,000 was primarily due to lower interest rates and a decrease in investment balances as compared to 2010.

Interest Expense. Interest expense decreased to $221,000 for the year ended December 31, 2011 from $644,000 in 2010. This decrease of $423,000 was due to the debt under the credit and security agreement with GE Healthcare Financial Services being paid in full in July 2011.

Liquidity and Capital Resources

Since inception, our operations have been financed primarily through the sale of equity securities. Through December 31, 2012, we received net proceeds of approximately $463.6 million from the sale of shares of our preferred and common stock as follows:

- from September 12, 2002 to December 31, 2006, we issued and sold a total of 1,053,572 shares of common stock for aggregate net proceeds of $14,801;
- in March 2004, we issued and sold a total of 9,322,035 shares of Series A redeemable convertible preferred stock for aggregate net proceeds of $9.2 million and the conversion of promissory notes and interest thereon totaling $1.7 million;
- from April 2005 to May 2005, we issued and sold 14,830,509 shares of Series B redeemable convertible preferred stock for aggregate net proceeds of $34.9 million;
- in November 2006, we issued and sold a total of 8,771,930 shares of Series C convertible preferred stock for aggregate net proceeds of $29.9 million;
- in May 2007, we issued and sold a total of 8,050,000 shares of common stock for aggregate net proceeds of $87.9 million;

- in January and February 2008, we issued and sold a total of 7,326,435 shares of common stock for aggregate net proceeds of $74.9 million; and
- in July 2009, we issued and sold a total of 11,500,000 shares of common stock for aggregate net proceeds of $81.6 million; and
- in December 2011, we issued and sold a total of 5,646,173 shares of common stock and common stock warrants to purchase up to 56,461,730 shares for aggregate net proceeds of $86.9 million; and
- in October 2012, we issued and sold a total of 11,000,000 shares of common stock for aggregate net proceeds of $56.5 million.

As of December 31, 2012, we had $78.3 million in cash and cash equivalents and an additional $59.1 million in investment securities, available-for-sale. As of December 31, 2012, our holdings primarily consisted of treasury-backed money market funds, treasuries and other instruments that are insured, guaranteed or supported by the U.S. federal government. We maintain established guidelines relating to diversification and maturities of our investments to preserve principal and maintain liquidity.

Net cash used in operating activities was $68.3 million and $29.2 million for 2012 and 2011, respectively. Net cash used in each of these periods was primarily a result of external research and development expenses, clinical trial costs, personnel-related costs, third-party supplier and manufacturer expenses and professional fees.

Net cash used in investing activities was $13.3 million for 2012 and the net cash provided by investing activities was $21.1 million for 2011. These amounts are primarily the result of the net purchases and maturities of investment securities.

Net cash provided by financing activities was $58.3 million and $85.0 million for 2012 and 2011, respectively. The net cash provided by financing activities for 2012 is primarily as a result of the public sale of our common stock in October 2012 for aggregate net proceeds of $56.5 million. The net cash provided by financing activities for 2011 is primarily as a result of the public sale of our common stock and warrants in December 2011 for aggregate net proceeds of $86.9 million.

We cannot be certain if, when or to what extent we will receive cash inflows from the commercialization of our product candidates. We will incur substantial additional development expenses to conduct the Light Study for Contrave and to develop Empatic. We initiated the Light Study in June 2012. Prior to its commencement, we anticipated that the costs to conduct the Light Study to the interim analysis would be approximately $100.0 million. We believe the costs we have incurred to date and expect to incur in the future in connection with the conduct of the Light Study are consistent with our original projection. Until we finalize any future development plans for Empatic, including based on additional feedback from the FDA and our ability to secure a collaboration partner, we are not able to estimate the expenses required to further develop Empatic.

We have entered into license agreements to acquire the rights to develop and commercialize Contrave and Empatic. Pursuant to these agreements, we obtained exclusive and non-exclusive licenses to the patent rights and know-how for selected indications and territories. Under our license agreement with Duke University, we issued 442,624 shares of our common stock in March 2004 and may be required to make future milestone payments totaling up to $1.7 million upon the achievement of various milestones related to regulatory or commercial events. Under our license agreement with Lee Dante, M.D., we issued an option to purchase 73,448 shares of our common stock in April 2004. We also paid Dr. Dante an upfront fee of $100,000 and, in September 2010, we paid him an additional $1.0 million upon the execution of the collaboration agreement with Takeda. In the future, we may be obligated to pay royalties to Dr. Dante related to certain revenues we receive in connection with any sublicense agreements we enter into, including our collaboration agreement with Takeda. Under our license agreement with Oregon Health & Science University, we issued 76,315 shares of our common stock in December 2003 and paid an upfront fee of $65,000. Under these three agreements, we are also obligated to pay royalties on any net sales of the licensed products.

Our future capital uses and requirements depend on numerous factors. These factors include but are not limited to the following:

- the rate of progress and cost of the Light Study, and the scope, cost and timing of any additional clinical trials required for Contrave and clinical trials for Empatic, including expenses to support the trials and milestone payments that may become payable, and the decisions we make with respect to the continued development of such product candidates;
- the extent to which we in-license, acquire or invest in other indications, products, technologies and businesses;
- the terms and timing of any collaborative, licensing, co-promotion or other arrangements that we may establish with respect to Contrave or Empatic;
- the costs of establishing sales, marketing and distribution capabilities in order to commercialize Contrave if and when it is approved for marketing, should we elect to do so;
- the costs involved in enforcing or defending patent claims or other intellectual property rights;
- the costs and timing of regulatory approvals for Contrave and Empatic, if at all; and
- the successful commercialization of our products, if approved.

Although it is difficult to predict future liquidity requirements, we believe that our existing cash and cash equivalents and investment securities, available-for-sale will be sufficient to meet our projected operating requirements through the next 12 months.

Until we can generate significant cash from our operations, we expect to continue to fund our operations with existing cash resources, proceeds of potential offerings of our equity securities, debt, potential milestone payments under existing our existing collaboration agreement, receivables or royalty financings and potential future corporate collaborations and licensing arrangements. However, we cannot be sure that our existing cash and investment resources will be adequate, that additional financing will be available when needed or that, if available, financing will be obtained on terms favorable to us or our stockholders. Having insufficient funds may require us to delay, scale back or eliminate some or all of our development programs and/or our pre-commercialization and commercialization activities, relinquish some or even all rights to product candidates or renegotiate less favorable terms than we would otherwise choose. Failure to obtain adequate financing also may adversely affect our ability to operate as a going concern. If we raise additional funds by issuing equity securities, substantial dilution to existing stockholders would likely result. Debt, receivables and royalty financings may be coupled with an equity component, such as warrants to purchase stock, which could also result in dilution of our existing stockholders' ownership. If we raise additional funds through debt, receivables or royalty financings, the terms of such financings may involve significant cash payment obligations as well as covenants and specific financial requirements that may restrict our ability to operate our business.

Continued turbulence in the U.S. and international markets and economies may adversely affect our ability to obtain additional financing on terms acceptable to us, or at all. If these market conditions continue, they may limit our ability to access the capital markets to meet liquidity needs.

Contractual Obligations and Commitments

The following table describes our long-term contractual obligations and commitments as of December 31, 2012 (in thousands):

	Payments Due by Periods				
	Total	Less Than 1 Year	1-3 Years	4-5 Years	After
Operating lease obligations	$726	$ 726	$ —	$ —	$—
Total	$726	$ 726	$ —	$ —	$—

We have not included certain license obligations which may require additional payments of up to $1.7 million due upon the occurrence of certain milestones related to regulatory or commercial events. We may also be required to pay royalties on any net sales of the licensed products. License payments may increase based on the timing of various milestones and the extent to which the licensed technologies are pursued for other indications. These milestone payments and royalty payments under our license agreements are not included in the table above because we cannot, at this time, determine when or if the related milestones will be achieved or the events triggering the commencement of payment obligations will occur. We have not included any lease obligations related to the amendment we entered into in February 2013 to extend the lease for our corporate headquarters for an additional 4 years to September 2017.

We also enter into agreements with third parties to manufacture our product candidates, conduct our clinical trials and perform data collection and analysis. Our payment obligations under these agreements depend upon the progress of our development programs. Therefore, we are unable at this time to estimate with certainty the future costs we will incur under these agreements.

Recently Issued Accounting Standards

In December 2011, the Financial Accounting Standards Board ("FASB") issued Accounting Standards Update ("ASU") 2011-11, Balance Sheet (Topic 210): Disclosures about Offsetting Assets and Liabilities (ASU 2011-11). This newly issued accounting standard requires an entity to disclose both gross and net information about instruments and transactions eligible for offset in the statement of financial position as well as instruments and transactions executed under a master netting or similar arrangement and was issued to enable users of financial statements to understand the effects or potential effects of those arrangements on its financial position. ASU 2011-11 is required to be applied retrospectively and is effective for fiscal years, and interim periods within those years, beginning on or after January 1, 2013. As this accounting standard only requires enhanced disclosure, we do not expect the adoption of this standard to have a material impact on our financial statements.

In June 2011, the FASB issued ASU No. 2011-05, *Comprehensive Income* (Topic 220) ("ASU No. 2011-05"). ASU No. 2011-05 amends the presentation of comprehensive income to allow an entity the option to present the total of comprehensive income, the components of net income, or the components of other comprehensive income either in a single continuous statement of comprehensive income or in two separate but consecutive statements. In both choices, an entity is required to present each component of net income along with total net income, each component of other comprehensive income along with a total for other comprehensive income, and a total amount for comprehensive income. ASU No. 2011-05 eliminates the option to present the components of other comprehensive income as part of the statement of changes in stockholders' equity. ASU No. 2011-05 is effective on a retrospective basis for fiscal years, and interim periods within those years, beginning after December 15, 2011. The retrospective application had only a presentation impact on our financial statements for the twelve months ended December 31, 2012.

Off-Balance Sheet Arrangements

We have not engaged in any off-balance sheet activities.

Item 7A. Quantitative and Qualitative Disclosures About Mar ket Risk

Our cash and cash equivalents and investment securities, available-for-sale, as of December 31, 2012 consisted primarily of money market funds, U.S. government agency securities and corporate debt obligations. We do not have any auction rate securities on our balance sheet, as they are not permitted by our investment policy. Our primary exposure to market risk is interest income sensitivity, which is affected by changes in the general level of U.S. interest rates, particularly because the majority of our investments are in short-term marketable debt securities. The primary objective of our investment activities is to preserve principal while at the same time maximizing the income we receive from our investments without significantly increasing risk. Some

of the securities that we invest in may be subject to market risk. This means that a change in prevailing interest rates may cause the value of the investment to fluctuate. For example, if we purchase a security that was issued with a fixed interest rate and the prevailing interest rate later rises, the value of our investment will probably decline. To minimize this risk, we intend to continue to maintain our portfolio of cash equivalents and short-term investments in a variety of securities including commercial paper, money market funds and government and non-government debt securities, all with various maturities. In general, money market funds are not subject to market risk because the interest paid on such funds fluctuates with the prevailing interest rate.

Our cash is invested in accordance with an investment policy approved by our board of directors which specifies the categories, allocations, and ratings of securities we may consider for investment. We do not believe our cash, cash equivalents and investment securities have significant risk of default or illiquidity. We made this determination based on discussions with our investment advisors and a review of our holdings. While we believe our cash, cash equivalents and investment securities are well diversified and do not contain excessive risk, we cannot provide assurance that in the future our investments will not be subject to adverse changes in market value.

In addition, domestic and international equity markets have experienced and may continue to experience heightened volatility and turmoil based on domestic and international economic conditions and concerns. In the event these economic conditions and concerns continue and the markets continue to remain volatile, our results of operations could be adversely affected by those factors in many ways, including making it more difficult for us to raise funds if necessary and our stock price may further decline. In addition, we maintain significant amounts of cash and cash equivalents that are not federally insured. If economic instability continues, we cannot provide assurance that we will not experience losses on these investments.

Item 8. Financial Statements and Supplementary Data

Index to Financial Statements

REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

The Board of Directors and Stockholders of
Orexigen Therapeutics, Inc.

We have audited the accompanying balance sheets of Orexigen Therapeutics, Inc. as of December 31, 2012 and 2011, and the related statements of operations, comprehensive loss, stockholders' equity, and cash flows for each of the three years in the period ended December 31, 2012. 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 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. An audit also includes assessing the accounting principles used and significant estimates made by management, as well as evaluating the overall financial statement presentation. We believe that our audits provide a reasonable basis for our opinion.

In our opinion, the financial statements referred to above present fairly, in all material respects, the financial position of Orexigen Therapeutics, Inc. at December 31, 2012 and 2011, and the results of its operations and its cash flows for each of the three years in the period ended December 31, 2012, in conformity with U.S. generally accepted accounting principles.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States), Orexigen Therapeutics, Inc.'s internal control over financial reporting as of December 31, 2012, based on criteria established in Internal Control-Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission and our report dated March 14, 2013 expressed an unqualified opinion thereon.

/s/ Ernst & Young LLP

San Diego, California
March 14, 2013

OREXIGEN THERAPEUTICS, INC.

BALANCE SHEETS
(In thousands, except share and par value amounts)

	December 31, 2012	December 31, 2011
ASSETS		
Current assets:		
Cash and cash equivalents	$ 78,332	$ 101,749
Investment securities, available-for-sale	59,071	45,844
Prepaid expenses and other current assets	1,491	1,126
Total current assets	138,894	148,719
Property and equipment, net	83	439
Restricted cash	177	542
Total assets	$139,154	$ 149,700
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 3,811	$ 1,532
Accrued clinical trial expenses	13,529	155
Accrued expenses	4,345	2,590
Deferred revenue, current portion	3,429	3,429
Total current liabilities	25,114	7,706
Deferred revenue, less current portion	38,571	42,000
Other long-term liabilities	—	288
Commitments and contingencies		
Stockholders' equity:		
Preferred stock, $.001 par value, 10,000,000 shares authorized at December 31, 2012 and 2011, no shares issued and outstanding at December 31, 2012 and 2011	—	—
Common stock, $.001 par value, 300,000,000 shares authorized at December 31, 2012 and 2011; 84,413,670 and 61,285,514 shares issued and outstanding at December 31, 2012 and 2011, respectively	84	61
Additional paid-in capital	512,174	446,357
Accumulated other comprehensive income (loss)	15	(2)
Accumulated deficit	(436,804)	(346,710)
Total stockholders' equity	75,469	99,706
Total liabilities and stockholders' equity	$139,154	$ 149,700

See accompanying notes.

OREXIGEN THERAPEUTICS, INC.

STATEMENTS OF OPERATIONS
(In thousands, except per share amounts)

	Years Ended December 31,		
	2012	2011	2010
Revenues:			
Collaborative agreement	$ 3,428	$ 3,428	$ 1,143
License revenue	—	971	88
Total revenues	3,428	4,399	1,231
Operating expenses:			
Research and development	73,680	12,780	28,131
General and administrative	19,987	19,502	24,495
Total operating expenses	93,667	32,282	52,626
Loss from operations	(90,239)	(27,883)	(51,395)
Other income (expense):			
Interest income	147	46	124
Interest expense	(2)	(221)	(644)
Total other income (expense)	145	(175)	(520)
Net loss	$ (90,094)	$ (28,058)	$ (51,915)
Net loss per share—basic and diluted	$ (1.27)	$ (0.58)	$ (1.10)
Shares used to compute basic and diluted net loss per share	70,739	48,273	47,377

See accompanying notes.

OREXIGEN THERAPEUTICS, INC.

STATEMENTS OF COMPREHENSIVE LOSS
(In thousands)

	Years Ended December 31,		
	2012	2011	2010
Net Loss	$(90,094)	$(28,058)	$(51,915)
Other comprehensive income (loss)			
Unrealized gains (losses) on investment securities	17	7	(3)
Other comprehensive income (loss)	17	7	(3)
Comprehensive loss	$(90,077)	$(28,051)	$(51,918)

See accompanying notes.

OREXIGEN THERAPEUTICS, INC.

STATEMENTS OF STOCKHOLDERS' EQUITY
(In thousands)

	Common Stock		Additional Paid-In Capital	Accumulated Other Comprehensive Income (Loss)	Accumulated Deficit	Total Stockholders' Equity
	Shares	Amount				
Balance at December 31, 2009	47,215	$ 47	$342,599	$ (6)	$(266,737)	$ 75,903
Exercise of common stock options	552	1	1,490	—	—	1,491
Stock-based compensation expense	—	—	8,312	—	—	8,312
Unrealized loss on securities, available-for-sale	—	—	—	(3)	—	(3)
Net loss					(51,915)	(51,915)
Balance at December 31, 2010	47,767	48	352,401	(9)	(318,652)	33,788
Issuance of common stock and warrants, net of issuance costs	5,646	5	86,906	—	—	86,911
Net exercise of warrants	7,555	7	—	—	—	7
Exercise of common stock options	317	1	451	—	—	452
Stock-based compensation expense	—	—	6,599	—	—	6,599
Unrealized gain on securities, available-for-sale	—	—	—	7	—	7
Net loss					(28,058)	(28,058)
Balance at December 31, 2011	61,285	61	446,357	(2)	(346,710)	99,706
Issuance of common stock, net of issuance costs	11,000	11	56,520	—	—	56,531
Net exercise of warrants	11,131	11	—	—	—	11
Exercise of common stock options	998	1	1,727	—	—	1,728
Stock-based compensation expense	—	—	7,570	—	—	7,570
Unrealized gain on securities, available-for-sale	—	—	—	17	—	17
Net loss					(90,094)	(90,094)
Balance at December 31, 2012	84,414	$ 84	$ 512,174	$ 15	$ (436,804)	$ 75,469

See accompanying notes.

OREXIGEN THERAPEUTICS, INC.

STATEMENTS OF CASH FLOWS
(In thousands)

	Years Ended December 31,		
	2012	2011	2010
Operating activities			
Net loss	$ (90,094)	$ (28,058)	$(51,915)
Adjustments to reconcile net loss to net cash provided by (used in) operating activities:			
Amortization of premium (accretion of discount) on investment securities, available-for-sale	500	870	1,024
Amortization of debt issuance costs	—	191	296
Depreciation	313	443	473
Loss on disposal of equipment	42	12	2
Stock-based compensation	7,570	6,599	8,312
Changes in operating assets and liabilities:			
Prepaid expenses and other current assets	(365)	1,376	(973)
Accounts payable and accrued expenses	17,306	(6,078)	527
Other assets	—	12	48
Other long-term liabilities	—	(14)	(690)
Deferred rent	(186)	(157)	(109)
Deferred revenue	(3,428)	(4,399)	48,769
Net cash provided by (used in) operating activities	(68,342)	(29,203)	5,764
Investing activities			
Purchases of investment securities, available-for-sale	(78,921)	(73,041)	(100,842)
Maturities and sales of investment securities, available-for-sale	65,211	93,774	86,875
Purchases of property and equipment	—	—	(45)
Restricted cash	365	339	409
Net cash provided by (used in) investing activities	(13,345)	21,072	(13,603)
Financing activities			
Payments on borrowings on long-term debt	—	(2,416)	(6,384)
Proceeds from issuance of common stock and warrants	58,270	87,370	1,491
Net cash provided by (used in) financing activities	58,270	84,954	(4,893)
Increase (decrease) in cash and cash equivalents	(23,417)	76,823	(12,732)
Cash and cash equivalents at beginning of period	101,749	24,926	37,658
Cash and cash equivalents at end of period	$ 78,332	$101,749	$ 24,926
Supplemental Disclosure			
Interest paid	$ —	$ 29	$ 334
Unrealized gain (loss) on investment securities, available-for-sale	$ 17	$ 7	$ (3)

See accompanying notes.

OREXIGEN THERAPEUTICS, INC.
NOTES TO FINANCIAL STATEMENTS

1. Organization and Basis of Presentation

Orexigen Therapeutics, Inc. (the "Company"), a Delaware corporation, is a biopharmaceutical company focused on the development of pharmaceutical product candidates for the treatment of obesity. The Company was incorporated in September 2002 and commenced operations in 2003.

The Company's primary activities since incorporation have been organizational activities, including recruiting personnel, conducting research and development, including clinical trials, and raising capital. The Company has experienced losses since its inception, and as of December 31, 2012, had an accumulated deficit of $436.8 million. The Company expects to continue to incur losses for at least the next several years. Successful transition to attaining profitable operations is dependent upon achieving a level of revenues adequate to support the Company's cost structure, and until that time, the Company may need to continue to raise additional equity or debt financing.

2. Summary of Significant Accounting Policies

Use of Estimates

The preparation of financial statements in conformity with accounting principles generally accepted in the United States requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities and disclosure of contingent assets and liabilities at the date of the financial statements and the reported amounts of revenue and expenses during the reporting period. Actual results could differ from those estimates.

Cash and Cash Equivalents

The Company considers all highly liquid investments with maturities of three months or less from the date of purchase to be cash equivalents.

Investment Securities, Available-for-Sale

The Company classifies all investment securities as available-for-sale, as the sale of such securities may be required prior to maturity to implement management strategies. These investment securities are carried at fair value, with unrealized gains and losses reported as accumulated other comprehensive income (loss) until realized. The cost of debt securities is adjusted for amortization of premiums and accretion of discounts to maturity. Such amortization and accretion, as well as interest and dividends, are included in interest income. Realized gains and losses from the sale of available-for-sale securities, if any, are determined on a specific identification basis and are also included in interest income.

Restricted Cash

As of December 31, 2012, restricted cash represents certificates of deposit pledged as collateral for letters of credit issued by the Company in connection with the execution of operating leases.

Fair Value of Financial Instruments

The carrying amount of cash and cash equivalents, accounts payable and accrued expenses are considered to be representative of their respective fair value because of the short-term nature of these items. Investment securities, available-for-sale, are carried at fair value.

Concentration of Credit Risk

Financial instruments that potentially subject the Company to concentrations of credit risk consist primarily of cash and cash equivalents and investment securities, available-for-sale. The Company maintains deposits in federally insured financial institutions in excess of federally insured limits. However, management believes the Company is not exposed to significant credit risk due to the financial position of the depository institutions in which these deposits are held. Additionally, the Company has established guidelines regarding the diversification of its investments and their maturities, which are designed to maintain safety and liquidity.

Concentration of Revenue

Takeda Pharmaceutical Company Limited ("Takeda") accounted for 100%, 78% and 93% of revenue for the years ended December 31, 2012, 2011 and 2010, respectively. Cypress Bioscience, Inc. ("Cypress") accounted for 0%, 22% and 7% of revenue for the years ended December 31, 2012, 2011 and 2010, respectively.

Property and Equipment

Property and equipment is stated at cost and depreciated over the estimated useful lives of the assets (three to five years) using the straight-line method. Leasehold improvements are stated at cost and amortized over the shorter of their useful lives or the lease term.

Impairment of Long-Lived Assets

The Company will record impairment losses on long-lived assets used in operations when events and circumstances indicate that assets might be impaired and the undiscounted cash flows estimated to be generated by those assets are less than the carrying amount of those assets. While the Company's current and historical operating losses and cash flows are indicators of impairment, the Company believes the future cash flows to be received support the carrying value of its long-lived assets and, accordingly, the Company has not recognized any impairment losses as of December 31, 2012.

Research and Development Costs

All research and development costs are charged to expense as incurred and consist principally of costs related to clinical trials managed by the Company's contract research organizations, license fees and salaries and related benefits. Clinical trial costs are a significant component of research and development expenses. These costs are accrued based on estimates of work performed, and require estimates of total costs incurred based on patients enrolled, progress of clinical studies and other events. Clinical trial costs are subject to revision as the trials progress and revisions are charged to expense in the period in which they become known.

Patent Costs

All costs related to filing and pursuing patent applications are expensed as incurred as recoverability of such expenditures is uncertain.

Income Taxes

Deferred tax assets and liabilities are determined based on the differences between the financial reporting and tax basis of assets and liabilities using enacted tax rates which will be in effect when the differences reverse. The Company provides a valuation allowance against net deferred tax assets unless, based upon the available evidence, it is more likely than not that the deferred tax asset will be realized.

The Company follows the provisions of the Income Taxes Topic of the Financial Accounting Standards Board ("FASB") Accounting Standards Codification that defines a recognition threshold and measurement

attributes for the financial statement recognition and measurement of a tax position taken or expected to be taken in a tax return. Under the Income Taxes Topic, the impact of an uncertain income tax position on the income tax return must be recognized at the largest amount that is more-likely-than-not to be sustained upon audit by the relevant taxing authority. An uncertain income tax position will not be recognized if it has less than a 50% likelihood of being sustained.

Revenue Recognition

The Company has entered into agreements with Takeda Pharmaceutical Company Limited ("Takeda") and Cypress Bioscience, Inc. ("Cypress") which contain multiple elements, including nonrefundable upfront fees, payments for reimbursement of research costs, payments associated with achieving specific development milestones and royalties based on specified percentages of net product sales, if any.

Prior to the revised multiple element and milestone method of revenue recognition guidance adopted by the Company on January 1, 2011, nonrefundable, up-front license fees and milestone payments with standalone value that are not dependent on any future performance by the Company under the agreements were recognized as revenue upon the earlier of when payments are received or collection is assured, but were deferred if the Company has continuing performance obligations. If the Company had continuing involvement through contractual obligations under such agreements, such up-front fees were deferred and recognized over the period for which the Company continued to have a performance obligation. Both the Takeda and Cypress agreements had continuing obligations, and as a result the up-front fees were deferred upon receipt.

Effective January 1, 2011, for multiple element agreements entered into or materially modified after December 31, 2010, the Company follows the provisions of ASU No. 2009-13. During 2011, the Company did not enter into any new collaborations. In order to account for the multiple-element arrangements, the Company identifies the deliverables included within the agreement and evaluates which deliverables represent separate units of accounting. Analyzing the arrangement to identify deliverables requires the use of judgment, and each deliverable may be an obligation to deliver services, a right or license to use an asset, or another performance obligation. A delivered item is considered a separate unit of accounting when the delivered item has value to the partner on a standalone basis based on the consideration of the relevant facts and circumstances for each arrangement. Factors considered in this determination include the research capabilities of the partner and the availability of research expertise in this field in the general marketplace. Arrangement consideration is allocated at the inception of the agreement to all identified units of accounting based on their relative selling price. The relative selling price for each deliverable is determined using vendor-specific objective evidence ("VSOE") of selling price or third-party evidence of selling price if VSOE does not exist. If neither VSOE nor third-party evidence of selling price exists, we use our best estimate of the selling price for the deliverable. The amount of allocable arrangement consideration is limited to amounts that are fixed or determinable. The consideration received is allocated among the separate units of accounting, and the applicable revenue recognition criteria are applied to each of the separate units. Changes in the allocation of the sales price between delivered and undelivered elements can impact revenue recognition but do not change the total revenue recognized under any agreement. Upfront license fee payments are recognized upon delivery of the license if facts and circumstances dictate that the license has standalone value from the undelivered items, which generally include research and development services and the manufacture of drug products, the relative selling price allocation of the license is equal to or exceeds the upfront license fee, persuasive evidence of an arrangement exists, our price to the partner is fixed or determinable, and collectability is reasonably assured. The adoption of this new accounting standard did not have a material impact on the Company's results of operations or financial position.

Upfront license fee payments are deferred if facts and circumstances dictate that the license does not have standalone value. The determination of the length of the period over which to defer revenue is subject to judgment and estimation and can have a material impact on the amount of revenue recognized in a given period.

The terms of the Company's partnership agreements provide for milestone payments upon achievement of certain regulatory/development and sales-based events. Effective January 1, 2011, the Company adopted on a prospective basis the guidance under ASU No. 2010-17, "Revenue Recognition-Milestone Method". Under the Milestone Method of accounting, the Company recognizes consideration that is contingent upon the achievement of a milestone as revenue in the period in which the milestone is achieved only if the milestone is substantive. A milestone is considered substantive when it meets all of the following three criteria: 1) The consideration is commensurate with either the entity's performance to achieve the milestone or the enhancement of the value of the delivered item(s) as a result of a specific outcome resulting from the entity's performance to achieve the milestone, 2) The consideration relates solely to past performance, and 3) The consideration is reasonable relative to all of the deliverables and payment terms within the arrangement. A milestone is defined as an event (i) that can only be achieved based in whole or in part on either the entity's performance or on the occurrence of a specific outcome resulting from the entity's performance, (ii) for which there is substantive uncertainty at the date the arrangement is entered into that the event will be achieved and (iii) that would result in additional payments being due to the Company. The adoption of this new accounting standard did not have a material impact on the Company's results of operations or financial position.

Royalties to be received based on sales of the Company's licensed products by partners will be recognized as earned.

Stock-Based Compensation

Compensation costs related to all equity instruments granted are recognized at the grant-date fair value of the awards. Additionally, the Company includes an estimate of the number of awards that will be forfeited in calculating compensation costs, which is recognized over the requisite service period of the awards on a straight-line basis. No related tax benefits of the share-based compensation costs have been recognized since the Company's inception.

The fair value of each option award was estimated on the date of grant using the Black-Scholes option valuation model. The following weighted-average assumptions were utilized for the calculations during each period:

	Years Ended December 31,		
	2012	2011	2010
Expected life (in years)	6.0	6.0	6.0
Expected volatility	87.5%	76.0%	65.1%
Risk-free interest rate	1.1%	2.0%	2.4%
Expected dividend yield	0.0%	0.0%	0.0%
Per share grant-date fair value	$2.26	$ 1.38	$ 3.83

The weighted average expected life of options was calculated using the simplified method as prescribed by the Securities and Exchange Commission ("SEC"). This decision was based on the lack of relevant historical data due to the Company's limited historical experience. In addition, due to the Company's limited historical data, the estimated volatility incorporates the historical volatility of comparable companies whose share prices are publicly available. The risk-free interest rate assumption was based on the United States Treasury's rates for U.S. Treasury zero-coupon bonds with maturities similar to those of the expected term of the award being valued. The assumed dividend yield was based on the Company's expectation of not paying dividends in the foreseeable future.

Total stock-based compensation expense recognized during the years ended December 31, 2012, 2011 and 2010 was comprised of the following (in thousands):

	Years Ended December 31,		
	2012	2011	2010
General and administrative	$5,755	$ 5,003	$5,308
Research and development	1,815	1,596	3,004
	$ 7,570	$6,599	$8,312

At December 31, 2012, total unrecognized estimated share-based compensation expense related to non-vested stock options granted prior to that date was $24.6 million, which is expected to be recognized over a weighted-average period of 2.7 years.

Equity instruments issued to non-employees are recorded at their fair value and are periodically revalued as the equity instruments vest and are recognized as expense over the related service period. In connection with the issuance of options to purchase shares of common stock to non-employees, the Company recorded total stock-based compensation (included in the table above) within stockholders' equity totaling $0, $54,000 and $181,000 for the years ended December 31, 2012, 2011 and 2010, respectively.

Comprehensive Loss

The Company records all components of comprehensive income, including net income, in the financial statements in the period in which they are recognized. Comprehensive loss consists of net loss and certain changes in stockholders' equity that are excluded from net loss. Comprehensive loss for each of the years ended December 31, 2012, 2011 and 2010 has been reflected in the Statements of Comprehensive Loss. Accumulated other comprehensive income (loss), which is included in Stockholders' Equity, represents unrealized gains and losses on investment securities, available-for-sale.

Comprehensive loss includes net loss and unrealized gains and losses on investments. The Company discloses the accumulated balance of other comprehensive loss as a separate component of stockholder's equity.

Net Loss Per Share

Basic net loss per share is calculated by dividing the net loss by the weighted average number of common shares outstanding for the period less the weighted average number of shares subject to repurchase. Diluted net loss per share is computed by dividing the net loss by the weighted average number of basic shares plus common stock equivalents outstanding during the period determined using the treasury stock method, if dilutive. Stock options are considered to be common stock equivalents and were not included in the net loss per share calculation for the years ended December 31, 2012, 2011 and 2010 because the inclusion of such underlying shares would have had an anti-dilutive effect.

(In thousands, except per share amounts)	Years Ended December 31,		
	2012	2011	2010
Historical			
Numerator:			
Net loss	$(90,094)	$(28,058)	$(51,915)
Denominator:			
Weighted average common shares outstanding	70,739	48,273	47,377
Denominator for basic and diluted net loss per share	70,739	48,273	47,377
Net loss per share—basic and diluted	$ (1.27)	$ (0.58)	$ (1.10)

Historical outstanding anti-dilutive securities not included in the diluted net loss per share calculation include the following (in thousands):

	As of December 31,		
	2012	2011	2010
Common stock warrants outstanding	37,768	48,902	—
Common stock options outstanding	13,839	10,586	8,036
	51,607	59,488	8,036

Recently Issued Accounting Standards

In December 2011, the Financial Accounting Standards Board ("FASB") issued Accounting Standards Update ("ASU") 2011-11, Balance Sheet (Topic 210): Disclosures about Offsetting Assets and Liabilities (ASU 2011-11). This newly issued accounting standard requires an entity to disclose both gross and net information about instruments and transactions eligible for offset in the statement of financial position as well as instruments and transactions executed under a master netting or similar arrangement and was issued to enable users of financial statements to understand the effects or potential effects of those arrangements on its financial position. ASU 2011-11 is required to be applied retrospectively and is effective for fiscal years, and interim periods within those years, beginning on or after January 1, 2013. As this accounting standard only requires enhanced disclosure, the Company does not expect the adoption of this standard to have a material impact on the Company's financial statements.

In June 2011, the FASB issued ASU No. 2011-05, *Comprehensive Income* (Topic 220) ("ASU No. 2011-05"). ASU No. 2011-05 amends the presentation of comprehensive income to allow an entity the option to present the total of comprehensive income, the components of net income, or the components of other comprehensive income either in a single continuous statement of comprehensive income or in two separate but consecutive statements. In both choices, an entity is required to present each component of net income along with total net income, each component of other comprehensive income along with a total for other comprehensive income, and a total amount for comprehensive income. ASU No. 2011-05 eliminates the option to present the components of other comprehensive income as part of the statement of changes in stockholders' equity. ASU No. 2011-05 is effective on a retrospective basis for fiscal years, and interim periods within those years, beginning after December 15, 2011. The retrospective application had only a presentation impact on the Company's financial statements for the twelve months ended December 31, 2012.

3. Investment Securities, Available-for-Sale

The Company invests its excess cash in investment securities, principally debt instruments of financial institutions, corporations with investment grade credit ratings and government agencies. Regardless of maturity date, the Company intends to use all available-for-sale securities in current operations, therefore these assets have been classified as short-term. A summary of the estimated fair value of investment securities, available-for-sale, is as follows at December 31, 2012 and December 31, 2011 (in thousands):

December 31, 2012	Maturity in Years	Amortized Cost	Unrealized Gains	Unrealized Losses	Fair Value
U.S. government agency securities	Less than 1	$ 49,923	$ 14	$ —	$ 49,937
U.S. government agency securities	1 to 2	9,133	1	—	9,134
Total investment securities		$59,056	$15	$ —	$59,071

December 31, 2011	Maturity in Years	Amortized Cost	Unrealized Gains	Unrealized Losses	Fair Value
Corporate debt obligations	Less than 1	$16,819	$ 3	$ (5)	$16,817
U.S. Treasury securities	Less than 1	3,276	1	—	3,277
U.S. government agency securities	Less than 1	25,749	4	(3)	25,750
Total investment securities		$ 45,844	$ 8	$ (8)	$ 45,844

Gross realized gains and losses on available-for-sale securities were immaterial during the years ended December 31, 2012, 2011 and 2010.

4. Fair Value Measurements

The following table presents information about the Company's financial assets measured at fair value on a recurring basis as of December 31, 2012, and indicates the fair value hierarchy of the valuation techniques utilized by the Company 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 that the Company has the ability to access. The Company classifies money market funds as Level 1 assets. Fair values determined by Level 2 inputs utilize inputs other than quoted prices included in Level 1 that are observable for the asset or liability, either directly or indirectly. Level 2 inputs include quoted prices for similar assets and liabilities in active markets, and inputs other than quoted prices that are observable for the asset or liability, such as interest rates and yield curves that are observable at commonly quoted intervals. The Company classifies commercial paper holdings, U.S. Treasury securities, U. S. government agency securities and asset-backed security holdings as Level 2 assets. Level 3 inputs are unobservable inputs for the asset or liability, and include situations where there is little, if any, market activity for the asset or liability. The Company does not hold any Level 3 assets. In certain cases, the inputs used to measure fair value may fall into different levels of the fair value hierarchy. In such cases, the level in the fair value hierarchy within which the fair value measurement in its entirety falls has been determined based on the lowest level input that is significant to the fair value measurement in its entirety. The Company's assessment of the significance of a particular input to the fair value measurement in its entirety requires judgment, and considers factors specific to the asset or liability.

Assets that have recurring measurements are shown below (in thousands):

		Fair Value Measurement at Reporting Date Using		
Description	Balance as of December 31, 2012	Quoted Prices in Active Markets for Identical Assets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Financial instruments owned:				
Cash and money market funds	$ 78,332	$ 78,332	$ —	$ —
U.S. government agency securities	59,071	—	59,071	—
Total financial instruments owned	$ 137,403	$ 78,332	$ 59,071	$ —

		Fair Value Measurement at Reporting Date Using		
Description	Balance as of December 31, 2011	Quoted Prices in Active Markets for Identical Assets (Level 1)	Significant Other Observable Inputs (Level 2)	Significant Unobservable Inputs (Level 3)
Financial instruments owned:				
Cash and money market funds	$ 91,184	$ 91,184	$ —	$ —
U.S. Treasury securities	3,277	—	3,277	—
Corporate debt obligations	16,817	—	16,817	—
U.S. government agency securities	36,315	—	36,315	—
Total financial instruments owned	$147,593	$ 91,184	$ 56,409	$ —

5. Property and Equipment

Property and equipment consists of the following (in thousands):

	Useful Life in Years	December 31, 2012	December 31, 2011
Furniture and fixtures	5	$ 1,079	$ 1,102
Computer equipment and software	3 to 5	447	447
Leasehold improvements	5	435	555
Laboratory equipment	5	—	32
		1,961	2,136
Accumulated depreciation		(1,878)	(1,697)
Property and equipment, net		$ 83	$ 439

Depreciation expense was $313,000, $443,000 and $473,000 for each of the years ended December 31, 2012, 2011 and 2010, respectively.

6. Accrued Expenses

Accrued expenses consist of the following (in thousands):

	December 31, 2012	December 31, 2011
Accrued compensation related expenses	$3,960	$2,186
Accrued legal and professional expenses	113	174
Other accrued expenses	272	230
	$ 4,345	$2,590

7. Commitments and Contingencies

Credit and Security Agreement

In December 2006, the Company entered into a Credit and Security Agreement with Merrill Lynch Capital (the "Credit Agreement") which, as amended provided for potential borrowing until December 31, 2008 of up to $25.0 million. The Company was required to make monthly payments of principal and interest and all amounts outstanding under the Credit Agreement became due and payable on July 1, 2011, at which time the debt was paid in full and terminated.

Operating Leases

In December 2007, the Company entered into an operating lease agreement for office facilities (corporate headquarters) in San Diego, California. The term of the lease began in April 2008 and is for an initial term of 64 months. The monthly rental payments are adjusted on an annual basis. As security for the lease, the landlord required a letter of credit for $1.0 million. The letter of credit is collateralized by a certificate of deposit of $177,000, which is included in restricted cash in the accompanying balance sheet at December 31, 2012. Rent expense is being recorded on a straight-line basis over the life of the lease. In September 2008, the Company entered into an amendment to lease to expand the office space at this location by 9,312 square feet. The initial term of the lease for this expanded space was for 52 months and began in April 2009. The monthly rental payments were adjusted on an annual basis. Rent expense was being recorded on a straight-line basis over the life of the lease for the expanded space. In March 2012, the Company entered into a Partial Lease Termination Agreement with its landlord pursuant to which the Company will decrease the office space at its corporate

headquarters, by 9,312 rentable square feet thereby decreasing its total leased space to approximately 22,229 rentable square feet. The Agreement provides for, among other things, a one-time payment of $190,849 by the Company to the landlord and termination of the Company's payment obligations with respect to the terminated premises.

Future minimum payments under the operating leases as of December 31, 2012 are as follows (in thousands):

Years Ending December 31,	
2013	$726
2014	—
	$726

Total rent expense for each of the years ended December 31, 2012, 2011 and 2010 was approximately $1.4 million, $1.6 million and $1.5 million, respectively.

Technology and License Agreements

Takeda Pharmaceutical Company Limited

In September 2010, the Company entered into a collaboration agreement with Takeda to develop and commercialize Contrave in the United States, Canada and Mexico. Under the terms of the collaboration agreement, the Company received a nonrefundable upfront cash payment of $50.0 million from Takeda and is eligible to receive additional payments of over $1.0 billion upon achieving certain anniversary, regulatory/development and sales-based milestones, including $100.0 million that can be achieved between the regulatory approval and the first commercial sale of Contrave in the United States. The Company is also eligible to receive tiered royalty payments ranging from a minimum of 20% to a maximum of 35%, subject to customary reductions, on increasing levels of net sales in the United States, Canada and Mexico. In accordance with the Company's continuing performance obligation of the collaboration, the upfront payment of $50.0 million is being deferred and recognized over 14.5 years, the estimated term of the agreement. For the years ended December 31, 2012, 2011 and 2010, the Company recognized revenues under this agreement of $3.4 million, $3.4 million and $1.1 million, respectively. At December 31, 2012 and 2011, deferred revenue under this agreement totaled $42.0 million and $45.4 million, respectively. Also the Company recorded receivables at December 31, 2012 and 2011 for approximately $14,000 and $65,000, respectively, for reimbursement by Takeda for certain commercial and patent costs permitted under the collaboration agreement, which were accounted for as a reduction of the expenses reimbursed.

The Company has assessed milestones under the revised authoritative guidance for research and development milestones and determined that two regulatory/development milestone payments, $20.0 million due to the Company upon regulatory approval in the United States and $10.0 million due to the Company upon the delivery of launch supplies to Takeda, meet the definition of a milestone as 1) they are events that can only be achieved in part on the Company's performance or upon the occurrence of a specific outcome resulting in the Company's performance, (2) there was substantive uncertainty at the date the agreement was entered into that the event will be achieved, and (3) they result in additional payments being due to the Company. The third regulatory/development milestone payment, $70.0 million due to the Company upon the first commercial sale in the United States, does not meet the definition of a milestone as Takeda is responsible for the commercialization of Contrave. Sales-based milestone payments currently do not meet these criteria and will not be classified as milestones as their achievement is solely based on the performance of Takeda. The Company has determined that the anniversary milestones do not meet the definition of a milestone as the Company believes these payments are contingent solely upon the passage of time.

Oregon Health & Science University

In June 2003, the Company entered into a license agreement with Oregon Health & Science University ("OHSU"), whereby the Company acquired an assignment of any rights OHSU may have to a U.S. provisional patent application that the Company filed, which formed the basis for the Company's subsequently issued patents. This license agreement was amended in November 2003, December 2006 and December 2007. As consideration for this license agreement, the Company paid an upfront fee of $65,000 and issued 76,315 shares of the Company's common stock to OHSU. The Company is also obligated to pay a royalty to OHSU on net sales for Contrave and any other products covered by the assigned patent rights. At December 31, 2012, no royalty payments have been made or are payable under this agreement as the product has not been launched and sales have not commenced. The Company is also responsible for all prosecution and maintenance (including all costs associated with the enforcement) of any patent applications, that stem from these assigned rights, and for any patents that have or may issue with respect thereto.

OHSU has also licensed to the Company, on an exclusive basis, the issued patent underlying the *in vitro* model that the Company has used for screening combination therapies for impact on neuronal activity. With respect to these rights, the Company was required to make a payment of $20,000 upon receipt of a pair of mice and is required to pay an additional $20,000 upon receipt of any additional pair of mice. OHSU is solely responsible for the prosecution, maintenance and enforcement (including all costs associated therewith) of this patent; however the Company is required to pay 100% of expenses incurred by OHSU in the maintenance and prosecution of this patent. As of December 31, 2012, the Company has paid a total of approximately $118,000 in connection with the maintenance and prosecution of this patent. In addition, OHSU has the right to not file any patent application or to abandon any patent or patent application included in the patent rights, in which case it must provide the Company 60 days' prior written notice and, in response, the Company may elect at its sole cost to pursue these actions. The Company's rights to this patent extend through the expiration of the patent, which is expected to occur in 2024.

The Company has assessed milestones under the revised authoritative guidance for research and development milestones and determined that two regulatory/development milestone payments, $20.0 million due to the Company upon regulatory approval in the United States and $10.0 million due to the Company upon the delivery of launch supplies to Takeda, meet the definition of a substantive milestone. The third regulatory/development milestone payment, $70.0 million due to the Company upon the first commercial sale in the United States, does not meet the definition of a milestone as Takeda is responsible for the commercialization of Contrave. Sales-based milestone payments also do not meet these criteria and will not be classified as milestones as their achievement is solely based on the performance of Takeda. The Company has determined that the anniversary milestones do not meet the definition of a substantive milestone as the Company believes these payments are contingent solely upon the passage of time.

Duke University

In March 2004, the Company entered into a patent license agreement (the "Duke Agreement") with Duke University ("Duke") whereby the Company acquired, among other things, an exclusive worldwide license to a U.S. patent. As consideration for this license, the Company issued 442,624 shares of its common stock to Duke and may be required to make future milestone payments totaling $1.7 million upon the achievement of various milestones related to regulatory or commercial events. The Company is also obligated to pay a royalty on net sales of products covered by the license. The Company has the right to grant sublicenses to third parties, subject to an obligation to pay Duke a royalty on any revenue it receives under such sublicensing arrangements. In addition, the Company is obligated to pay Duke a specified royalty on sales of products which are covered by certain of the Company's issued patents under the OHSU license agreement. At December 31, 2012, no such payments have been made or are payable under the Duke Agreement as the product has not been launched and sales have not commenced. In January 2005, the Company sublicensed the technology to Cypress for a non-refundable upfront payment of $1.5 million. In January 2011, Cypress exercised its right to terminate the agreement.

The term of the Duke Agreement generally extends until the last licensed patent right expires, which is expected to occur in 2023. Either party may terminate the agreement upon delivery of written notice if the other party commits fraud, willful misconduct, or illegal conduct of the other party with respect to the subject matter of the agreement. In addition, either party may terminate the agreement upon delivery of written notice if the other party commits a material breach of its obligations and fails to remedy the breach within a specified period. The Company may also voluntarily terminate the agreement upon delivery of written notice within a specified time period. Duke may terminate the agreement upon delivery of written notice if the Company fails to meet certain specified milestones of the agreement and fail to remedy such a breach within the specified period. In addition, Duke may terminate the agreement upon specified bankruptcy, liquidation or receivership proceedings.

Lee Dante, M.D.

In June 2004, the Company entered into a patent license agreement with Lee G. Dante, M.D. whereby the Company acquired an exclusive worldwide license to two U.S. patents. As consideration for this license, the Company paid upfront fees totaling $100,000 and granted Dr. Dante an option to purchase 73,448 shares of its common stock. The Company is also obligated to pay a royalty on net sales of products covered by the license. In September 2010, the Company entered into an amendment to this license agreement with Dr. Dante pursuant to which the Company agreed to, among other things, provide for a payment to Dr. Dante in the amount of $1 million upon the execution of its collaboration agreement with Takeda. The payment was made by the Company in September 2010 and has been reported as research and development expense. The Company has the right to grant sublicenses of the patented technology to third parties, subject to its obligation to pay Dr. Dante a royalty on any revenue it receives from such arrangements.

The term of the agreement generally extends until the last licensed patent right expires, which is expected to occur in 2013. Either party may terminate the agreement upon delivery of written notice if the other party commits fraud, willful misconduct, or illegal conduct with respect to the subject matter of the agreement. In addition, either party may terminate the agreement upon delivery of written notice if the other party commits a material breach of its obligations and fails to remedy the breach within a specified period. The Company may also voluntarily terminate the agreement upon delivery of written notice within a specified time period. In addition, Dr. Dante may terminate the agreement upon specified bankruptcy, liquidation or receivership proceedings.

Cypress Bioscience, Inc.

In January 2005, the Company entered into a license agreement with Cypress whereby the Company sublicensed certain of its rights under a patent license agreement with Duke to Cypress for specified uses. As consideration for this license, Cypress paid the Company non-refundable upfront fees of $1.5 million. Cypress can require the Company to provide clinical support for any of the specified uses over the term of the agreement. Accordingly, this $1.5 million was initially recognized over 17 years, the estimated life of the sublicensed patent. In January 2011, Cypress exercised its right to terminate the agreement. The remaining deferred revenue was recognized in the quarter ending March 31, 2011.

For each of the years ended December 31, 2012, 2011 and 2010, the Company recognized revenues under this agreement of $0, $971,000 and $88,000. At December 31, 2012 and 2011, deferred revenue under this agreement totaled $0 and $0, respectively.

8. Stockholders' Equity

Common Stock and Common Stock Warrants

In December 2011, the Company completed a public offering of 5,646,173 units. Each unit consists of one share of common stock and a warrant to purchase ten shares of common stock, at a price to the public of $1.45 per share of common stock and $1.449 per warrant to purchase each share of common stock, which

together comprise the purchase price of $15.94 per unit. Net cash proceeds from the public offering were $86.9 million, after deducting underwriting discounts and commissions and offering expenses. The warrants issued in the transaction have an exercise price equal to $0.001 per share. Each warrant is exercisable in whole or in part for a period of 10 years commencing on December 22, 2011. A holder of a warrant will not have the right to exercise any portion of the warrant if such holder (together with its affiliates) would beneficially own in excess of 9.99% of the number of shares of the Company's common stock outstanding immediately after giving effect to the exercise of such warrant. These warrants may only be exercised pursuant to a cashless net exercise, whereby the exercise price of the warrants is satisfied through the reduction in shares issued upon exercise equal in value to the exercise price. There are no provisions in the warrant agreement which would require the Company to settle the warrants through the distribution of cash. The initial warrants provided for the purchase of up to 56,461,730 shares. A total of 11,130,548 and 7,554,649 shares were issued upon warrant exercises in the 2012 and 2011, respectively. Warrants to purchase an aggregate of up to 37,767,900 and 48,902,310 shares were outstanding as of December 31, 2012 and 2011, respectively.

In October 2012, the Company completed a public offering of 11,000,000 shares of its common stock at a public offering price of $5.50 per share. Net cash proceeds from the public offering were approximately $56.5 million, after deducting underwriting discounts and commissions and offering expenses payable by the Company.

As of December 31, 2012, the Company had 300,000,000 authorized shares of common stock.

Stock Options

During 2004, the Company adopted the 2004 Stock Plan (the "2004 Plan") under which, as amended, 3,159,275 shares of common stock are reserved for issuance to employees, directors and consultants of the Company. The 2004 Plan provides for the grant of incentive stock options, non-statutory stock options and rights to purchase restricted stock to eligible recipients. Recipients of incentive stock options shall be eligible to purchase shares of the Company's common stock at an exercise price equal to no less than the estimated fair market value of such stock on the date of grant. The maximum term of options granted under the 2004 Plan is ten years. The options generally vest over four years, and some are immediately exercisable. At December 31, 2012, no stock options are outstanding under the 2004 Plan.

In February 2007, the Company's stockholders approved the 2007 Equity Incentive Award Plan (the "2007 Plan"), which became effective in April 2007, under which 3,525,000 shares of common stock were initially reserved for future issuance to employees, directors and consultants of the Company. Effective January 1, 2009, 2010 and 2011, the Board of Directors increased the shares available for issuance under the 2007 Plan by 1,721,666, 2,000,000 and 2,000,000 shares, respectively, in accordance with an "evergreen" provision. The 2007 Plan provides for the issuance of stock options, stock appreciation rights, restricted stock units, performance stock units, and other stock-based awards. The 2007 Plan has an initial term of ten years. As of the effectiveness of the 2007 Plan, no additional shares will be granted under the 2004 Plan. The 2007 Plan was amended in October 2009 and February 2010 to provide for the reservation of 500,000 and 2,000,000 shares, respectively, of the Company's common stock to be used exclusively for the grant of awards to individuals not previously an employee or non-employee director of the Company (or following a bona fide period of non-employment with the Company), as an inducement material to the individual's entering into employment with the Company within the meaning of Rule 5635(c)(4) of the NASDAQ Listing Rules. In June 2011, the 2007 Plan was amended to, among other things, add an additional 10,000,000 shares to the number of shares of common stock authorized for issuance under the 2007 Plan, increase the number of shares to be added to the 2007 Plan automatically each January 1, starting with January 1, 2012, to the least of (i) 15% of the Company's outstanding common stock on the applicable January 1, (ii) 6,000,000 shares of common stock and (iii) a lesser number of shares of the Company's common stock determined by the Company's board of directors, and increase the limitation on the number of shares that may be granted pursuant to the exercise of incentive stock option to 40,000,000 shares. At December 31, 2012, options to purchase 13,838,894 shares have been granted and are outstanding under the 2007 Plan.

In June 2011, to provide incentive to the employees of the Company to continue their employment, the Company announced an option exchange program. Under the exchange program, eligible optionholders had an opportunity to exchange eligible stock options for a new stock option issued under the Company's 2007 equity incentive award plan. The exercise price of the new option was $1.66 per share, which was the closing price of the Company's common stock as reported by the Nasdaq Global Market on the first business day after the expiration date of the exchange offer. New options granted to employees vest over four years, with the shares vesting in equal monthly installments over 48 months. On July 22, 2011, the eligible optionholders exchanged options exercisable for an aggregate of 7,407,634 shares of common stock in the program. On July 25, 2011, the Company issued new stock options exercisable for an aggregate of 7,407,634 shares of common stock with an exercise price of $1.66 per share. As a result of the option exchange program, the Company will recognize additional stock-based compensation expense of $2.7 million over the four year vesting period of the new stock options.

In March 2011, to provide incentive to the employees of the Company to continue their employment while its management and Board worked to update the Company's corporate strategy, the Compensation Committee of the Company's Board of Directors approved an amendment to certain outstanding option grants to provide for a one-time repricing of the exercise price of such options to purchase shares of the Company's common stock held by employees (the "Repricing"). The Repricing affected an aggregate of 1,443,150 shares of the Company's common stock subject to outstanding option grants (the "Affected Grants"). An aggregate of 492,357 shares subject to the Affected Grants had an original exercise price of $5.89 (the "September 2010 Grants") and the remaining 950,793 shares had an exercise price of $9.31 (the "January 2011 Grants"). The vesting commencement date for both the September 2010 Grants and the January 2011 Grants was January 18, 2011. The Compensation Committee chose to amend the September 2010 Grants and the January 2011 Grants because they believed that the amendment of these grants would achieve the desired retentive affect for the Company's employees given the circumstances around the Company's recent corporate realignment. The exercise price of all Affected Grants was amended in the Repricing to $2.94, the closing price of the Company's common stock on March 2, 2011. As a result of the Repricing, the Company will recognize additional stock-based compensation expense of $819,000 over the four year vesting period of the Affected Grants.

The following table summarizes stock option activity for the 2004 and 2007 Plans:

	Number of Options	Weighted Average Exercise Price
Outstanding at December 31, 2009	7,008,037	$ 6.13
Granted	2,424,568	6.32
Exercised	(551,834)	2.61
Forfeited	(844,944)	8.76
Outstanding at December 31, 2010	8,035,827	6.15
Granted	13,235,806	2.41
Exercised	(317,379)	1.43
Forfeited/Cancelled	(10,367,875)	5.12
Outstanding at December 31, 2011	10,586,379	1.92
Granted	4,268,125	3.10
Exercised	(997,608)	1.74
Forfeited	(18,002)	3.44
Outstanding at December 31, 2012	13,838,894	$ 2.29

The following table summarizes information about stock options outstanding under the 2007 Plan at December 31, 2012:

	Options Outstanding			Options Exercisable	
Range of Exercise Prices	Number of Options	Weighted Average Remaining Contractual Life (In Years)	Weighted Average Exercise Price	Number of Options	Weighted Average Exercise Price
$1.61 - $1.66	6,575,348	8.6	$ 1.66	1,739,990	$ 1.66
$1.67 - $2.58	5,079,018	8.8	$ 2.18	1,461,265	$ 2.09
$2.59 - $8.18	2,184,528	8.1	$ 4.47	892,991	$ 4.80
$1.61 - $8.18	13,838,894	8.6	$ 2.29	4,094,246	$ 2.50

As of December 31, 2012, the aggregate intrinsic value of options outstanding and exercisable was approximately $41.5 million and $11.8 million, respectively. The aggregate intrinsic value of options exercised was $4.6 million, $531,000 and $2.1 million during the year ended December 31, 2012, 2011 and 2010, respectively. At December 31, 2012, the weighted average remaining contractual term for options exercisable was 8.1 years.

Common stock reserved for future issuance consists of the following at December 31, 2012:

Common stock warrants	37,767,900
Stock options issued and outstanding	13,838,894
Authorized for future option grants	7,617,479
	59,224,273

9. Income Taxes

Significant components of the Company's deferred tax assets at December 31, 2012 and 2011 are shown below. A valuation allowance has been recognized to offset the net deferred tax assets as realization of such deferred tax assets has not met the more likely than not threshold.

	December 31,	
(In thousands)	2012	2011
Deferred tax assets:		
Net operating loss carryforwards	$ 10,130	$ 4,970
Research and development credits	2,005	1,730
Capitalized research and development expenditures	28,939	13
Deferred revenue	17,113	18,487
Stock-based compensation	5,830	4,073
Other, net	1,284	(41)
Valuation allowance	(65,301)	(29,232)
	$ —	$ —

A reconciliation of income taxes to the amount computed by applying the statutory federal income tax rate to the net loss is summarized as follows:

(In thousands)	December 31, 2012	2011	2010
Income tax expense (benefit) at statutory rates	$(31,532)	$ (9,820)	$(18,170)
State income tax, net of federal benefit	(5,073)	(1,190)	(2,669)
Permanent items	428	540	466
Research and development credits	(344)	(885)	(1,499)
Stock-based compensation	447	2,251	1,215
Removal of net operating losses and research and development credits	—	110,861	—
Change in valuation allowance—eliminated net operating losses and R&D credits	—	(110,861)	—
Change in valuation allowance	36,074	9,104	20,657
Income tax expense (benefit)	$ —	$ —	$ —

At December 31, 2012, the Company has federal and state net operating loss carryforwards of approximately $289.0 million and $266.0 million, respectively. The federal and state loss carryforwards begin to expire in 2024 and 2015, respectively, unless previously utilized. At December 31, 2012, the Company has federal and state research and development tax credits of $12.0 million and $3.9 million, respectively. The federal research and development tax credits begin to expire in 2024 unless previously utilized and the state tax credits carry forward indefinitely.

Approximately $10.0 million of the net operating loss carryforwards relate to excess tax deductions for stock compensation, the income tax benefit of which will be recorded as additional paid-in-capital if and when realized.

Additionally, the utilization of the net operating loss and research and development tax credit carryforwards is subject to an annual limitation under Section 382 and 383 of the Internal Revenue Code of 1986, and similar state tax provisions due to ownership change limitations that have occurred previously or that could occur in the future. These ownership changes limit the amount of the net operating loss and research and development tax credit carryforwards and other deferred tax assets that can be utilized to offset future taxable income and tax, respectively. In general, an ownership change, as defined by Section 382 and 383, results from transactions increasing ownership of certain stockholders or public groups in the stock of the corporation by more than 50 percentage points over a three-year period. Although the Company has determined that more likely than not an ownership change has occurred in December 2012, the Company has not completed a formal update of its Section 382 analysis subsequent to December 31, 2010. Until this analysis has been updated, the Company has removed deferred tax assets for net operating losses of $505.4 million and research and development credits of $9.6 million from its deferred tax asset schedule and has recorded a corresponding decrease to its valuation allowance. When this analysis is finalized, the Company will reassess the amount of net operating losses and credits subject to limitation under Section 382. Due to the existence of the valuation allowance, future changes in the deferred tax assets related to these tax attributes will not impact the Company’s effective tax rate.

The following table summarizes the activity related to the Company's gross unrecognized tax benefits at the beginning and end of the years ended December 31, 2012, 2011 and 2010 (in thousands):

	December 31,		
	2012	2011	2010
Gross unrecognized tax benefits at the beginning of the year	$ 3,134	$2,935	$2,599
Increases related to current year tax positions	105	212	348
Decreases related to prior year tax positions	—	(13)	(12)
Expiration of unrecognized tax benefits	—	—	—
Gross unrecognized tax benefits at the end of the year	$3,239	$ 3,134	$ 2,935

Due to the valuation allowance, none of the unrecognized tax benefits as of December 31, 2012, if recognized, would reduce the Company's annual effective tax rate. The Company does not expect its unrecognized tax benefits to change significantly over the next 12 months.

The Company files income tax returns in the United States and in various state jurisdictions with varying statutes of limitations. Due to net operating losses incurred, the Company's tax returns from inception to date are subject to examination by taxing authorities. The Company's policy is to recognize interest expense and penalties related to income tax matters as a component of income tax expense. As of December 31, 2012, the Company had no interest or penalties accrued for uncertain tax positions.

The American Taxpayer Relief Act of 2012, which reinstated the United States federal research and development tax credit retroactively from January 1, 2012 through December 31, 2013, was not enacted into law until the first quarter of 2013. The law change will have no impact on the 2013 financial statements due to the valuation allowance placed against the Company's net deferred tax assets.

10. Litigation

The Company is not currently a party to any material legal proceedings.

11. Employee Benefit Plan

The Company has a defined contribution 401(k) retirement plan which allows employees to contribute up to 100% of their annual compensation up to the maximum annual amount prescribed by the Internal Revenue Service. The Company may elect to make a discretionary contribution or match a discretionary percentage of employee contributions. During the years ended December 31, 2012, 2011 and 2010, the Company's matching contributions to the plan were approximately $153,000, $158,000 and $264,000 respectively.

12. Subsequent Event

In February 2013, the Company entered into an amendment to extend the lease for its corporate headquarters for an additional 4 years to September 2017. In addition, the Landlord agreed to abate the Company's obligation to pay 50% of the Company's monthly basic rent for the first full nine months of the extension term and agreed to provide up to $311,206 for tenant improvements.

13. Selected Quarterly Financial Data (Unaudited)

The following financial information reflects all normal recurring adjustments, which are, in the opinion of management, necessary for a fair statement of the results of the interim periods. Selected quarterly financial data for years ended December 31, 2012 and 2011 are as follows (in thousands, except per share amounts):

	Year Ended December 31, 2012			
	1st Quarter	2nd Quarter	3rd Quarter	4th Quarter
Selected quarterly financial data:				
Revenues	$ 857	$ 857	$ 857	$ 857
Total operating expenses	11,312	17,564	31,457	33,334
Net loss	(10,414)	(16,661)	(30,564)	(32,455)
Net loss per share—basic and diluted (1)	$ (0.16)	$ (0.25)	$ (0.44)	$ (0.41)

	Year Ended December 31, 2011			
	1st Quarter	2nd Quarter	3rd Quarter	4th Quarter
Selected quarterly financial data:				
Revenues	$ 1,828	$ 857	$ 857	$ 857
Total operating expenses	13,326	8,335	5,446	5,175
Net loss	(11,603)	(7,568)	(4,580)	(4,307)
Net loss per share—basic and diluted (1)	$ (0.24)	$ (0.16)	$ (0.10)	$ (0.09)

(1) Net loss per share is computed independently for each of the quarters presented. Therefore, the sum of the quarterly net loss per share will not necessarily equal the total for the year.

Item 9. Changes in and Disagreements with Accountants on Accounting and Financial Disclosure.

None.

Item 9A. Controls and Procedures.

We maintain disclosure controls and procedures that are designed to ensure that information required to be disclosed in our Exchange Act reports is recorded, processed, summarized and reported within the time periods specified in the Securities and Exchange Commission's rules and forms and that such information is accumulated and communicated to our management, including our Chief Executive Officer and Chief Financial Officer, as appropriate, to allow for timely decisions regarding required disclosure. In designing and evaluating the disclosure controls and procedures, management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving the desired control objectives, and management is required to apply its judgment in evaluating the cost-benefit relationship of possible controls and procedures.

As required by Securities and Exchange Commission Rule 13a-15(b), we carried out an evaluation, under the supervision and with the participation of our management, including our Chief Executive Officer and Chief Financial Officer, of the effectiveness of the design and operation of our disclosure controls and procedures as of the end of the period covered by this report. Based on the foregoing, our Chief Executive Officer and Chief Financial Officer concluded that our disclosure controls and procedures were effective at the reasonable assurance level.

Management's Report on Internal Control Over Financial Reporting

Internal control over financial reporting refers to the process designed by, or under the supervision of, our Chief Executive Officer and Chief Financial Officer, and effected by our board of directors, management and other personnel, to provide reasonable assurance regarding the reliability of financial reporting and the

preparation of financial statements for external purposes in accordance with generally accepted accounting principles, and includes those policies and procedures that: (1) pertain to the maintenance of records that in reasonable detail accurately and fairly reflect the transactions and dispositions of our assets; (2) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that our receipts and expenditures are being made only in accordance with authorizations of our management and directors; and (3) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use or disposition of the company's assets that could have a material effect on the financial statements.

Internal control over financial reporting cannot provide absolute assurance of achieving financial reporting objectives because of its inherent limitations. Internal control over financial reporting is a process that involves human diligence and compliance and is subject to lapses in judgment and breakdowns resulting from human failures. Internal control over financial reporting also can be circumvented by collusion or improper management override. Because of such limitations, there is a risk that material misstatements may not be prevented or detected on a timely basis by internal control over financial reporting. However, these inherent limitations are known features of the financial reporting process. Therefore, it is possible to design into the process safeguards to reduce, though not eliminate, this risk.

Management is responsible for establishing and maintaining adequate internal control over our financial reporting, as such term is defined in Rule 13a-15(f) under the Exchange Act. Under the supervision and with the participation of our management, including our chief executive officer and chief financial officer, we conducted an evaluation of the effectiveness of our internal control over financial reporting. Management has used the framework set forth in the report entitled "Internal Control—Integrated Framework" published by the Committee of Sponsoring Organizations of the Treadway Commission to evaluate the effectiveness of our internal control over financial reporting. Based on its evaluation, management has concluded that our internal control over financial reporting was effective as of December 31, 2012, the end of our most recent fiscal year. Ernst & Young LLP, our independent registered public accounting firm, has issued a report on the effectiveness of our internal control over financial reporting, which is included below.

There has been no change in our internal control over financial reporting during the last fiscal quarter that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

Report of Independent Registered Public Accounting Firm

The Board of Directors and Stockholders of Orexigen Therapeutics, Inc.

We have audited Orexigen Therapeutics, Inc.'s internal control over financial reporting as of December 31, 2012, based on criteria established in Internal Control—Integrated Framework issued by the Committee of Sponsoring Organizations of the Treadway Commission (the COSO criteria). Orexigen Therapeutics, Inc.'s management is responsible for maintaining effective internal control over financial reporting, and for its assessment of the effectiveness of internal control over financial reporting included in the accompanying Management's Report on Internal Control Over Financial Reporting. Our responsibility is to express an opinion on the company's internal control over financial reporting based on our audit.

We conducted our audit 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 effective internal control over financial reporting was maintained in all material respects. Our audit included obtaining an understanding of internal control over financial reporting, assessing the risk that a material weakness exists, testing and evaluating the design and operating effectiveness of internal control based on the assessed risk, and performing such other procedures as we considered necessary in the circumstances. We believe that our audit provides a reasonable basis for our opinion.

A company's internal control over financial reporting is a process designed to provide reasonable assurance regarding the reliability of financial reporting and the preparation of financial statements for external purposes in accordance with generally accepted accounting principles. A company's internal control over financial reporting includes those policies and procedures that (1) pertain to the maintenance of records that, in reasonable detail, accurately and fairly reflect the transactions and dispositions of the assets of the company; (2) provide reasonable assurance that transactions are recorded as necessary to permit preparation of financial statements in accordance with generally accepted accounting principles, and that receipts and expenditures of the company are being made only in accordance with authorizations of management and directors of the company; and (3) provide reasonable assurance regarding prevention or timely detection of unauthorized acquisition, use, or disposition of the company's assets that could have a material effect on the financial statements.

Because of its inherent limitations, internal control over financial reporting may not prevent or detect misstatements. Also, projections of any evaluation of effectiveness to future periods are subject to the risk that controls may become inadequate because of changes in conditions, or that the degree of compliance with the policies or procedures may deteriorate.

In our opinion, Orexigen Therapeutics, Inc. maintained, in all material respects, effective internal control over financial reporting as of December 31, 2012, based on the COSO criteria.

We also have audited, in accordance with the standards of the Public Company Accounting Oversight Board (United States), the balance sheets of Orexigen Therapeutics, Inc. as of December 31, 2012 and 2011, and the related statements of operations, comprehensive loss, stockholders' equity, and cash flows for each of the three years in the period ended December 31, 2012 of Orexigen Therapeutics, Inc. and our report dated March 14, 2013 expressed an unqualified opinion thereon.

/s/ Ernst & Young LLP

San Diego, California
March 14, 2013

Item 9B. Other Information.

None.

PART III

Certain information required by Part III is omitted from this Annual Report on Form 10-K since we intend to file our definitive proxy statement for our 2013 annual meeting of stockholders, or the definitive proxy Statement, pursuant to Regulation 14A of the Securities Exchange Act of 1934, as amended, not later than 120 days after the end of the fiscal year covered by this Annual Report on Form 10-K, and certain information to be included in the Proxy Statement is incorporated herein by reference.

Item 10. Directors, Executive Officers and Corporate Governance.

Information regarding Directors, Executive Officers and Corporate Governance is hereby incorporated by reference to our definitive proxy statement, which will be filed with the SEC within 120 days after December 31, 2012.

We have adopted a Code of Business Conduct and Ethics that applies to our officers, directors and employees which is available on our internet website at www.orexigen.com. The Code of Business Conduct and Ethics contains general guidelines for conducting the business of our company consistent with the highest standards of business ethics, and is intended to qualify as a "code of ethics" within the meaning of Section 406 of the Sarbanes-Oxley Act of 2002 and Item 406 of Regulation S-K. In addition, we intend to promptly disclose (1) the nature of any amendment to our Code of Business Conduct and Ethics that applies to our principal executive officer, principal financial officer, principal accounting officer or controller or persons performing similar functions and (2) the nature of any waiver, including an implicit waiver, from a provision of our code of ethics that is granted to one of these specified officers, the name of such person who is granted the waiver and the date of the waiver on our website in the future.

Item 11. Executive Compensation.

Information regarding Executive Compensation is hereby incorporated by reference to our definitive proxy statement.

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

Information regarding Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters is hereby incorporated by reference to our definitive proxy statement.

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

Information regarding Certain Relationships and Related Transactions, and Director Independence is hereby incorporated by reference to our definitive proxy statement.

Item 14. Principal Accounting Fees and Services.

Information regarding the Principal Accounting Fees and Services is hereby incorporated by reference to our definitive proxy statement.

PART IV

Item 15. Exhibits, Financial Statement Schedules.

(a) Documents filed as part of this report:

1. The following financial statements of Orexigen Therapeutics, Inc. are filed as part of this report under Item 8—Financial Statements and Supplementary Data:

2. List of financial statement schedules. All schedules are omitted because they are not applicable or the required information is shown in the financial statements or notes thereto.

3. List of Exhibits required by Item 601 of Regulation S-K. See paragraph (b) below.

(b) The following exhibits are filed as part of this report:

Exhibit Number	Description
3.1[1]	Amended and Restated Certificate of Incorporation of the Registrant
3.2[7]	Certificate of Amendment of Amended and Restated Certificate of Incorporation of the Registrant
3.3[1]	Amended and Restated Bylaws of the Registrant
4.1[1]	Form of the Registrant's Common Stock Certificate
4.2[1]	Second Amended and Restated Investors' Rights Agreement dated November 20, 2006
4.3[2]	Registration Rights Waiver and Amendment dated January 6, 2008
4.4[16]	Form of Warrant to Purchase Common Stock
10.1[1]	Form of Director and Executive Officer Indemnification Agreement
10.2#[6]	Form of Executive Officer Employment Agreement
10.3#[1]	2004 Stock Plan and forms of option agreements thereunder
10.4#[7]	2007 Equity Incentive Award Plan, as amended, and forms of stock option grant notice and stock option agreement thereunder
10.5†[1]	License Agreement dated June 27, 2003 by and between the Registrant and Oregon Health & Science University
10.6†[1]	Amendment to License Agreement dated November 1, 2003 by and between the Registrant and Oregon Health & Science University
10.7†[1]	Letter Agreement Amendment to License Agreement dated December 6, 2003 by and between the Registrant and Oregon Health & Science University
10.8†[1]	License Agreement dated March 31, 2004 by and between the Registrant and Duke University
10.9†[1]	Amendment No. 1 to License Agreement dated December 22, 2004 by and between the Registrant and Duke University
10.10†[1]	Amendment No. 2 to License Agreement dated July 27, 2006 by and between the Registrant and Duke University
10.11†[1]	License Agreement dated June 1, 2004 by and between the Registrant and Lee G. Dante, M.D.
10.12[3]	Amendment No. 3 to License Agreement dated December 7, 2007 by and between the Registrant and Oregon Health & Science University
10.13[3]	Office Lease dated December 11, 2007 by and between the Registrant and Mullrock 3 Torrey Pines, LLC
10.14[4]	First Amendment to Lease dated September 23, 2008 by and between the Registrant and Mullrock 3 Torrey Pines, LLC
10.15†[5]	Naltrexone Hydrochloride Supply Agreement dated January 29, 2009 by and between the Registrant and Cilag GmbH International
10.16†[8]	Bupropion Hydrochloride Supply Agreement dated November 24, 2009 by and between the Registrant and Chemi, S.p.A.
10.17#[6]	Form of Chief Executive Officer Employment Agreement
10.18†[9]	Amended and Restated Master Agreement for Pharmaceutical Development Services dated March 12, 2010 by and between the Registrant and Patheon Pharmaceuticals, Inc.

Exhibit Number	Description
10.19†(9)	Manufacturing Services Agreement dated March 12, 2010 by and among the Registrant, Patheon Pharmaceuticals, Inc. and Patheon Inc.
10.20†(10)	Collaboration Agreement dated September 1, 2010 by and between the Registrant and Takeda Pharmaceutical Company Limited
10.21†(10)	Amendment No. 1 to License Agreement dated September 1, 2010 by and between the Registrant and Lee G. Dante
10.22†(17)	Amended and Restated License Agreement dated December 6, 2010 by and between the Registrant, GlaxoSmithKline LLC and Glaxo Group Limited
10.23#(11)	Separation Agreement dated February 16, 2011 by and between the Registrant and Graham K. Cooper
10.24#(12)	Orexigen Therapeutics, Inc. Key Executive Employee Retention Plan
10.25†(14)	Amendment No. 3 to the License Agreement dated June 8, 2011 by and between the Registrant and Duke University
10.26#(13)	Form of Second Amended and Restated Employment Agreement by and between the Registrant and Michael A. Narachi
10.27#(13)	Form of Amendment No.1 to Employment Agreement between the Registrant and Mark Booth
10.28#(15)	Amendment No. 2 to Amended and Restated Employment Agreement between Mark Booth and the Company dated November 1, 2011
10.29#(18)	Amendment No. 3 to Amended and Restated Employment Agreement dated March 15, 2012 by and between the Registrant and Mark Booth
10.30(19)	Partial Lease Termination Agreement dated March 2, 2012 by and between the Registrant and Mullrock 3 Torrey Pines, LLC
10.31#	Amended and Restated Independent Director Compensation Policy
23.1	Consent of Independent Registered Public Accounting Firm
31.1	Certification of Chief Executive Officer pursuant to Rule 13a-14 and Rule 15d-14 of the Securities Exchange Act of 1934, as amended
31.2	Certification of Chief Financial Officer pursuant to Rule 13a-14 and Rule 15d-14 of the Securities Exchange Act of 1934, as amended
32.1*	Certification of Chief Executive Officer and Chief Financial Officer pursuant to 18 U.S.C. 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002
101	The following financial statements and footnotes from the Orexigen Therapeutics, Inc. Annual Report on Form 10-K for the year ended December 31, 2012 formatted in eXtensible Business Reporting Language (XBRL): (i) Consolidated Balance Sheets; (ii) Consolidated Statements of Operations; (iii) Consolidated Statements of Comprehensive Loss; (iv) Consolidated Statements of Stockholders' Equity; (v) Consolidated Statements of Cash Flows; and (vi) the Notes to Condensed Consolidated Financial Statements

(1) Filed with the Registrant's Registration Statement on Form S-1 on December 19, 2006, as amended (File No. 333-139496).

(2) Filed with the Registrant's Current Report on Form 8-K on January 7, 2008.
(3) Filed with the Registrant's Current Report on Form 8-K on December 14, 2007.
(4) Filed with the Registrant's Quarterly Report on Form 10-Q on November 7, 2008.
(5) Filed with the Registrant's Annual Report on Form 10-K on March 13, 2009.
(6) Filed with the Registrant's Current Report on Form 8-K on January 28, 2010.
(7) Filed with the Registrant's Registration Statement on Form S-8 on June 22, 2011.
(8) Filed with the Registrant's Annual Report on Form 10-K on March 11, 2010.
(9) Filed with the Registrant's Quarterly Report on Form 10-Q on May 10, 2010.
(10) Filed with the Registrant's Quarterly Report on Form 10-Q on November 4, 2010.
(11) Filed with the Registrant's Current Report on Form 8-K on February 17, 2011.
(12) Filed with the Registrant's Current Report on Form 8-K on March 7, 2011.
(13) Filed with the Registrant's Current Report on Form 8-K on June 14, 2011.
(14) Filed with the Registrant's Quarterly Report on Form 10-Q on August 8, 2011.
(15) Filed with the Registrant's Current Report on Form 8-K on November 1, 2011.
(16) Filed with the Registrant's Current Report on Form 8-K on December 15, 2011.
(17) Filed with the Registrant's Annual Report on Form 10-K on March 11, 2011.
(18) Filed with the Registrant's Current Report on Form 8-K on March 16, 2012.
(19) Filed with the Registrant's Quarterly Report on Form 10-Q on May 10, 2012.

† Confidential treatment has been granted for portions of this exhibit. These portions have been omitted from the Registration Statement and filed separately with the Securities and Exchange Commission.

# Indicates management contract or compensatory plan.

* These certifications are being furnished solely to accompany this annual report pursuant to 18 U.S.C. Section 1350, and are not being filed for purposes of Section 18 of the Securities Exchange Act of 1934, as amended, and are not to be incorporated by reference into any filing of Orexigen Therapeutics, Inc., whether made before or after the date hereof, regardless of any general incorporation language in such filing.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, as amended, the registrant has duly caused this Annual Report on Form 10-K to be signed on its behalf by the undersigned, thereunto duly authorized.

OREXIGEN THERAPEUTICS, INC.

By: /s/ MICHAEL A. NARACHI
Michael A Narachi
President and Chief Executive Officer

Dated: March 14, 2013

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

Signature	Title	Date
/s/ MICHAEL A. NARACHI Michael A. Narachi	President and Chief Executive Officer Director (Principal Executive Officer)	March 14, 2013
/s/ JOSEPH P. HAGAN Joseph P. Hagan	Chief Business Officer (Principal Financial and Accounting Officer)	March 14, 2013
/s/ ECKARD WEBER Eckard Weber, M.D.	Chairman of the Board of Directors	March 14, 2013
/s/ LOUIS C. BOCK Louis C. Bock	Director	March 14, 2013
/s/ WENDY DIXON Wendy Dixon, Ph.D.	Director	March 14, 2013
/s/ BRIAN H. DOVEY Brian H. Dovey	Director	March 14, 2013
/s/ PETER K. HONIG Peter K. Honig, M.D.	Director	March 7, 2013
/s/ DAVID J. ENDICOTT David J. Endicott	Director	March 10, 2013
/s/ PATRICK MAHAFFY Patrick Mahaffy	Director	March 14, 2013
/s/ LOTA S. ZOTH Lota S. Zoth	Director	March 14, 2013

Exhibit 10.31

OREXIGEN THERAPEUTICS, INC.

INDEPENDENT DIRECTOR COMPENSATION POLICY

(AS AMENDED AND RESTATED EFFECTIVE NOVEMBER 29, 2012)

Non-employee members of the board of directors (the "***Board***") of Orexigen Therapeutics, Inc. (the "***Company***") shall be eligible to receive cash and equity compensation as set forth in this Independent Director Compensation Policy (this "***Policy***"). The cash compensation and option grants described in this Policy shall be paid or be made, as applicable, automatically and without further action of the Board, to each member of the Board who is not an employee of the Company or any parent or subsidiary of the Company (each, an "***Independent Director***") who may be eligible to receive such cash compensation or options, unless such Independent Director declines the receipt of such cash compensation or options by written notice to the Company. This Policy shall remain in effect until it is revised or rescinded by further action of the Board.

1. Cash Compensation.

Each Independent Director shall be eligible to receive an annual retainer of $35,000 for service on the Board. In addition, an Independent Director serving as:

(i) chairman of the Board shall be eligible to receive an additional annual retainer of $20,000 for such service;

(ii) chairman of the Audit Committee of the Board shall be eligible to receive an additional annual retainer of $18,000 for such service;

(iii) members (other than the chairman) of the Audit Committee shall be eligible to receive an additional annual retainer of $7,500 for such service;

(iv) chairman of the Compensation Committee of the Board shall be eligible to receive an additional annual retainer of $12,500 for such service;

(v) members (other than the chairman) of the Compensation Committee shall be eligible to receive an additional annual retainer of $5,000 for such service;

(vi) chairman of the Nominating/Corporate Governance Committee of the Board shall be eligible to receive an additional annual retainer of $7,500 for such service;

(vii) members (other than the chairman) of the Nominating/Corporate Governance Committee shall be eligible to receive an additional annual retainer of $3,750 for such service;

(viii) chairman of the Research and Development Strategy Committee shall be eligible to receive an additional annual retainer of $20,000 for such service; and

(ix) members (other than the chairman) of the Research and Development Strategy Committee shall be eligible to receive an additional annual retainer of $2,000 for such service.

The annual retainers shall be paid by the Company in quarterly installments or more frequently as deemed advisable by the officers of the Company for administrative or other reasons.

2. Equity Compensation. The options described below shall be granted under and shall be subject to the terms and provisions of the Company's 2007 Equity Incentive Award Plan (the "***2007 Plan***") and shall be granted subject to the execution and delivery of option agreements, including attached exhibits, in substantially the same forms previously approved by the Board, setting forth the vesting schedule applicable to such options and such other terms as may be required by the 2007 Plan.

(a) Initial Options. A person who is initially elected or appointed to the Board and who is an Independent Director at the time of such initial election or appointment, shall be eligible to receive a non-qualified stock option to purchase 35,000 shares of common stock (subject to adjustment as provided in the 2007 Plan) on the date of such initial election or appointment (each, an "***Initial Option***").

(b) Subsequent Options. A person who is an Independent Director automatically shall be eligible to receive a non-qualified stock option to purchase 35,000 shares of common stock (subject to adjustment as provided in the 2007 Plan) on the date of each annual meeting of the Company's stockholders. An Independent Director elected for the first time to the Board at an annual meeting of stockholders shall only receive an Initial Option in connection with such election, and shall not receive a Subsequent Option on the date of such meeting as well. The option grants described in the first sentence of this clause shall be referred to as "***Subsequent Options***." The Subsequent Option amount for an Independent Director elected for the first time to the Board prior to the annual meeting but after the previous year's annual meeting will be pro-rated to reflect the days that the Independent Director had served on the Board until the date of the annual meeting.

(c) Termination of Employment of Employee Directors. Members of the Board who are employees of the Company or any parent or subsidiary of the Company who subsequently terminate their employment with the Company and any parent or subsidiary of the Company and remain on the Board as Independent Directors will not receive an Initial Option grant pursuant to clause 2(a) above, but to the extent that they are otherwise eligible, will be eligible to receive, after termination from employment with the Company and any parent or subsidiary of the Company, Subsequent Options as described in clause 2(b) above.

(d) Terms of Options Granted to Independent Directors.

(i) Exercise Price. The per share exercise price of each option granted to an Independent Director shall equal 100% of the Fair Market Value (as defined in the 2007 Plan) of a share of common stock on the date the option is granted.

(ii) Vesting. Initial Options granted to Independent Directors shall vest and become exercisable in thirty-six equal monthly installments of 1/36 of the shares subject to such option on the same day of each one-month period of service as an Independent Director following the Initial Option grant, such that each Initial Option shall be 100% vested on the third (3rd) anniversary of the date of grant, subject to the Independent Director's continuing service on the Board through such dates. Subsequent Options granted to Independent Directors shall vest and become exercisable in twelve equal monthly installments of 1/12 of the shares subject to such option on the same day of each one-month period of service as an Independent Director following the Subsequent Option grant, such that each Subsequent Option shall be 100% vested on the first (1st) anniversary of the date of grant, subject to the Independent Director's continuing service on the Board through such dates. In addition, all Initial Options and Subsequent Options granted pursuant to this Policy shall vest and become exercisable in full in the event of a Change in Control (as defined in the 2007 Plan). No portion of an option which is unexercisable at the time of an Independent Director's termination of membership on the Board shall thereafter become exercisable.

(iii) Term. The term of each option granted to an Independent Director pursuant to this Independent Director Compensation Policy shall be ten years from the date the option is granted.

(iv) Effect of Termination of Board Service on Options. An Independent Director shall be able to exercise his or her Initial Options and Subsequent Options granted pursuant to this Policy and that were vested at the time of his or her cessation of Board service until the first to occur of (A) the third anniversary of the date of his or her cessation of Board service, or (B) the original expiration date of the term of such options.

Exhibit 23.1

CONSENT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

We consent to the incorporation by reference in the following Registration Statements:

(1) Registration Statements (Form S-3 No. 333-183918) of Orexigen Therapeutics, Inc. and

(2) Registration Statements (Form S-8 Nos. 333-142405, 333-165442 and 333-175071) pertaining to the Orexigen Therapeutics, Inc. 2007 Equity Incentive Plan and 2004 Stock Plan;

of our reports dated March 14, 2013, with respect to the financial statements of Orexigen Therapeutics, Inc. and the effectiveness of internal control over financial reporting of Orexigen Therapeutics, Inc., included in this Annual Report (Form 10-K) of Orexigen Therapeutics, Inc. for the year ended December 31, 2012.

/s/ Ernst & Young LLP

San Diego, California
March 14, 2013

Exhibit 31.1

CERTIFICATION OF PRINCIPAL EXECUTIVE OFFICER
PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002

I, Michael A. Narachi, certify that:

1. I have reviewed this annual report on Form 10-K of Orexigen Therapeutics, Inc.;

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

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

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

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

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

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

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

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

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

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

Date: March 14, 2013

/s/ MICHAEL A. NARACHI
Michael A. Narachi
President and Chief Executive Officer

Exhibit 31.2

CERTIFICATION OF PRINCIPAL FINANCIAL OFFICER
PURSUANT TO SECTION 302 OF THE SARBANES-OXLEY ACT OF 2002

I, Joseph P. Hagan, certify that:

1. I have reviewed this annual report on Form 10-K of Orexigen Therapeutics, Inc.;

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

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

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

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

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

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

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

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

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

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

Date: March 14, 2013

/s/ JOSEPH P. HAGAN
Joseph P. Hagan
Chief Business Officer

Exhibit 32.1

Certifications
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)

In connection with the Annual Report of Orexigen Therapeutics, Inc., a Delaware corporation (the "Company"), on Form 10-K for the period ended December 31, 2012, as filed with the Securities and Exchange Commission on the date hereof (the "Report"), I, Michael A. Narachi, President and Chief Executive Officer of the Company, certify, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that to my knowledge:

1. The Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934; and
2. The information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Dated: March 14, 2013

/s/ MICHAEL A. NARACHI

Michael A. Narachi
President and Chief Executive Officer
(principal executive officer of the registrant)

In connection with the Report, I, Joseph P. Hagan, Chief Business Officer of the Company, certify, pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002, that to my knowledge:

1. The Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934; and
2. The information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

Dated: March 14, 2013

/s/ JOSEPH P. HAGAN

Joseph P. Hagan
Chief Business Officer
(principal financial and accounting officer
of the registrant)

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