Vanda Pharmaceuticals Inc.
Form 10-K/A
April 29, 2009

UNITED STATES SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

Form 10-K/A

Amendment No. 1

þ	**ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934 For the fiscal year ended December 31, 2008**
o	**TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

Commission File No. 000-51863
VANDA PHARMACEUTICALS INC.
(Exact name of registrant as specified in its charter)

Delaware	**03-0491827**
(State or other jurisdiction of incorporation or organization)	*(I.R.S. Employer Identification No.)*

9605 Medical Center Drive, Suite 300
Rockville, Maryland 20850
(240) 599-4500
(Address and telephone number, including area code, of registrant s principal executive offices)

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

Title of Each Class	**Name of Each Exchange on Which Registered**
Common Stock, par value $0.001	The Nasdaq Stock Market LLC (NASDAQ Global Market)
Rights to Purchase Series A Junior Participating Preferred Stock	The Nasdaq Stock Market LLC (NASDAQ Global Market)

Securities registered pursuant to Section 12(g) of the Exchange 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 o No þ

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Exchange Act. Yes o No þ

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 þ No o

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 during the preceeding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes o No o

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. o

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 o	Accelerated filer þ	Non-accelerated filer o (Do not check if a smaller reporting company)	Smaller reporting company o

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Securities Exchange Act of 1934). Yes o No þ

The aggregate market value of the 17,756,198 shares of Common Stock held by non-affiliates of the registrant was $58,417,891 as of the last business day of the registrant s most recently completed second quarter based on the closing price of the registrant s Common Stock on such date. Shares of Common Stock held by each executive officer, director and stockholders known by the registrant to own 10% or more of the outstanding stock based on public filings and other information known to the registrant have been excluded since such persons may be deemed affiliates. This determination of affiliate status is not necessarily a conclusive determination for other purposes.

The number of shares of the registrant s Common Stock, par value $0.001 per share, outstanding as of April 15, 2009 was 26,653,478.

The exhibit index as required by Item 601(a) of Regulation S-K is included in Item 15 of Part IV of this report.

DOCUMENTS INCORPORATED BY REFERENCE: NONE

EXPLANATORY NOTE

Vanda Pharmaceuticals Inc. (the Company) is filing this amendment and restatement on Form 10-K/A to our Annual Report on Form 10-K for the fiscal year ended December 31, 2008, which was filed with the Securities and Exchange Commission (SEC) on March 13, 2009 (the Original Form 10-K) to (i) amend Items 10 through 14 of Part III of the Original Form 10-K to include the information required by such items because the Company s proxy statement relating to the 2009 annual meeting of stockholders will not be filed before April 30, 2009 (i.e. within 120 days after the end of the Company s 2008 fiscal year) and (ii) include the signature of PricewaterhouseCoopers LLP to the Report of Independent Registered Public Accounting Firm included in the Company s consolidated financial statements which signature was inadvertently not included in the Original Form 10-K. Certain portions of the Company s definitive proxy statement relating to the 2009 annual meeting of stockholders were initially incorporated by reference in Items 10 through 14 of Part III of the Original Form 10-K. References to our proxy statement on the cover page of this Form 10-K/A has been deleted and information with respect to the outstanding number of shares of common stock on the cover page of this Form 10-K/A has been updated. In addition, the Company s principal executive officer and principal financial officer are providing Rule 13a-14 certifications and written statements pursuant to Title 18 United States Code Section 1350, as added by Section 906 of the Sarbanes-Oxley Act of 2002.

Except for the foregoing amended information, this Form 10-K/A continues to speak as of the date of the Original Form 10-K, and the Company has not updated the disclosure contained herein to reflect any events that occurred at a later date other than that set forth above. All information contained in this Form 10-K/A is subject to updating and supplementing as provided in the Company s periodic reports filed with the SEC subsequent to the date of the filing of the Original Form 10-K.

Vanda Pharmaceuticals Inc.
Form 10-K/A

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PART I

CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS

Various statements in this report are forward-looking statements under the securities laws. Words such as, but not limited to, believe, expect, anticipate, estimate, intend, plan, targets, likely, will, would, and cou expressions or words, identify forward-looking statements. Forward-looking statements are based upon current expectations that involve risks, changes in circumstances, assumptions and uncertainties. Vanda Pharmaceuticals Inc. (We, Vanda or the Company) is at an early stage of development and may not ever have any products that generate significant revenue. Important factors that could cause actual results to differ materially from those reflected in our forward-looking statements include, among others:

- delays in the completion of our clinical trials;
- a failure of our product candidates to be demonstrably safe and effective;
- our failure to obtain regulatory approval for our products or to comply with ongoing regulatory requirements;
- a lack of acceptance of our product candidates in the marketplace, or a failure to become or remain profitable;
- our expectations regarding trends with respect to our costs and expenses;
- our inability to obtain the capital necessary to fund our research and development activities;
- our failure to identify or obtain rights to new product candidates;
- our failure to develop or obtain sales, marketing and distribution resources and expertise or to otherwise manage our growth;
- a loss of any of our key scientists or management personnel;
- losses incurred from product liability claims made against us; and
- a loss of rights to develop and commercialize our products under our license and sublicense agreements.

All written and verbal forward-looking statements attributable to us or any person acting on our behalf are expressly qualified in their entirety by the cautionary statements contained or referred to in this section. We caution investors not to rely too heavily on the forward-looking statements we make or that are made on our behalf. We undertake no obligation, and specifically decline any obligation, to update or revise publicly any forward-looking statements, whether as a result of new information, future events or otherwise.

We encourage you to read the discussion and analysis of our financial condition and our consolidated financial statements contained in this annual report on Form 10-K/A. We also encourage you to read Item 1A of Part 1 of this annual report on Form 10-K/A, entitled Risk Factors, which contains a more complete discussion of the risks and uncertainties associated with our business. In addition to the risks described above and in Item 1A of this report, other unknown or unpredictable factors also could affect our results. There can be no assurance that the actual results or developments anticipated by us will be realized or, even if substantially realized, that they will have the expected

consequences to, or effects on, us. Therefore no assurance can be given that the outcomes stated in such forward-looking statements and estimates will be achieved.

ITEM 1. BUSINESS

Overview

We are a biopharmaceutical company focused on the development and commercialization of clinical-stage drug candidates for central nervous system disorders, with exclusive worldwide commercial rights to two product candidates in clinical development. We believe that each of our product candidates will address a large market with significant unmet medical needs by offering advantages over currently available therapies. Our product portfolio includes:

Iloperidone, a compound for the treatment of schizophrenia. On November 27, 2007, the United States Food and Drug Administration (FDA) accepted a New Drug Application (NDA) for iloperidone for the treatment of schizophrenia. In July 2008, we announced that the FDA had determined that our NDA was not approvable and indicated, among other things, that we would have to conduct additional studies and submit that data before the FDA would approve iloperidone for commercial sale for the treatment of schizophrenia. In September 2008, we met with the FDA to discuss the FDA s determination. The FDA asked us to provide a complete response to the not-approvable letter, which we submitted on November 6, 2008. The FDA accepted our complete response for review and has set a new target action date of May 6, 2009. There are no guarantees that the FDA will provide its response by May 6, 2009, nor can there be any assurances that any such response will be favorable. Pending the FDA s reply to our complete response, we have suspended all non-essential iloperidone-related activities.

Tasimelteon, a compound for the treatment of sleep and mood disorders, including Circadian Rhythm Sleep Disorders (CRSD). In November 2006, Vanda announced positive top-line results from the Phase III trial of tasimelteon in transient insomnia. In June 2008, the Company announced positive top-line results from the Phase III trial of tasimelteon in chronic primary insomnia. We will have to conduct additional trials prior to our filing of an NDA for tasimelteon. Tasimelteon is also ready for Phase II trials for the treatment of depression. Pending a response from the FDA with respect to our NDA for iloperidone, Vanda is concentrating its efforts on the design and evaluation of clinical development options for tasimelteon.

We hold exclusive, worldwide rights to the above compounds and, assuming successful outcomes of our clinical trials and approval by the FDA, we expect to commercialize iloperidone with our own sales force and/or commercial partners in the United States and to seek partners for commercialization of the compound outside of the United States. Given the range of potential indications for tasimelteon, we intend to pursue one or more partnerships for the development and commercialization of tasimelteon worldwide.

On November 3, 2008, we received written notice from Novartis that the license agreement related to VSF-173, a compound for the treatment of excessive sleepiness that we had been developing, had terminated in accordance with its terms as a result of our failure to satisfy a specific development milestone within the time period specified in the license agreement. As a result, we no longer hold any rights with respect to VSF-173 and Novartis has a non-exclusive worldwide license to all information and intellectual property generated by or on behalf of Vanda related to its development of VSF-173. We are currently evaluating any options that we may have with respect to VSF-173, which may include the possibility of entering into a new license agreement or other arrangement with Novartis to allow us to resume our development of VSF-173; however, there can be no assurance that we will be able to enter into such an agreement or arrangement on acceptable terms, or at all.

Our founder and Chief Executive Officer, Mihael H. Polymeropoulos, M.D., started our operations early in 2003 after establishing and leading the Pharmacogenetics Department at Novartis AG (Novartis). In acquiring and developing our compounds we have relied upon our deep expertise in the scientific disciplines of pharmacogenetics and

pharmacogenomics. These scientific disciplines examine both genetic variations among people that influence response to a particular drug, and the multiple pathways through which drugs affect people. We believe that the combination of our expertise in these disciplines and our drug development expertise may provide us with preferential access to compounds discovered by other pharmaceutical

companies, and will allow us to identify new uses for these compounds. These capabilities should also enable us to shorten the time it takes to commercialize a drug when compared to traditional approaches.

Our two product candidates target large prescription markets with significant unmet medical needs. Sales of antipsychotic drugs were approximately $20 billion in 2007, according to Health Market Prognosis by IMS, a leading pharmaceutical market research company. These sales were achieved despite the safety concerns, moderate efficacy and poor patient compliance that are associated with these drugs. We believe that iloperidone may address some of the shortcomings of currently available drugs, based on its observed safety profile and the extended release injectable formulation for iloperidone that we plan to develop further. According to IMS, in 2006, sales of insomnia drugs generated more than $4 billion in worldwide sales and worldwide sales of anti-depressants exceeded $19 billion. However, approved drugs in both the sleep and mood disorders markets have sub-optimal safety and efficacy profiles. We believe tasimelteon may represent a breakthrough in each of these markets, based on the compound s demonstrated efficacy and safety to date and its novel mechanism of action.

Our strategy

Our goal is to create a leading biopharmaceutical company focused on developing and commercializing products that address critical unmet medical needs through the application of our drug development expertise and our pharmacogenetics and pharmacogenomics expertise. The key elements of our strategy to accomplish this goal are to:

Pursue the clinical development and regulatory approval of our current product candidates. On November 27, 2007, the FDA accepted the NDA for iloperidone for the treatment of schizophrenia. In July 2008, we announced that the FDA had determined that our NDA was not approvable. On November 6, 2008, we submitted a complete response to the not-approvable letter. The FDA has accepted the complete response for review and has set a new target action date of May 6, 2009. Pending the FDA s reply to our complete response, we have suspended all non-essential iloperidone-related activities. We have successfully completed a Phase III trial of tasimelteon in transient insomnia and announced positive top-line results in November 2006. In addition, we have successfully completed a Phase III trial of tasimelteon in chronic primary insomnia and announced positive top-line results in June 2008. We will need to conduct additional Phase III trials of tasimelteon in chronic sleep disorders prior to filing an NDA for this compound. Tasimelteon is also ready for Phase II trials for the treatment of depression.

Develop a focused commercialization capability in the United States. Because we believe that the number of physicians that would generate the majority of prescriptions in the United States for schizophrenia is relatively small, we believe that we can cost-effectively develop our own sales force to market and sell iloperidone in the United States.

Enter into partnerships to extend our commercial reach. We intend to seek commercial partners for iloperidone outside the United States and, even if we are able to develop our own sales force to market and sell iloperidone in the United States, we may decide to commercialize iloperidone in the United States with a partner, rather than on our own. In addition, given the range of potential indications for tasimelteon, we intend to pursue one or more partnerships for the development and commercialization of tasimelteon worldwide.

Apply our pharmacogenetics and pharmacogenomics expertise to differentiate our products. We believe that our pharmacogenetics and pharmacogenomics expertise will yield new insights into our product candidates. These insights may enable us to target our products to certain patient populations and to identify unexpected conditions for our product candidates to treat.

Expand our product portfolio through the identification and acquisition of additional compounds. We intend to continue to draw upon our clinical development expertise and pharmacogenetics and pharmacogenomics expertise to identify and pursue additional clinical-stage compounds.

Development programs

We have the following product candidates in clinical development:

Product Candidate	Target Indications	Clinical Status
Iloperidone (Oral)	Schizophrenia	Pending FDA decision; PDUFA date May 6, 2009
Iloperidone (Injectible)	Schizophrenia	Ready for Phase II trial
Tasimelteon	Sleep Disorders, including CRSD	Phase III trial for transient insomnia completed in 2006 Phase III trial for chronic primary insomnia completed in 2008
	Depression	Ready for Phase II trial

Iloperidone

We are developing iloperidone, a compound for the treatment of schizophrenia. The FDA accepted our NDA for iloperidone for the treatment of schizophrenia on November 27, 2007. The application included data from 35 clinical trials and more than 3,000 patients treated with iloperidone and also contains pharmacogenetic data aimed to further improve the benefit/risk profile of iloperidone in the treatment of patients with schizophrenia. In July 2008, we announced that the FDA had determined that our NDA for iloperidone was not approvable and indicated, among other things, that we would have to conduct additional studies and submit that data before the FDA would approve iloperidone for commercial sale for the treatment of schizophrenia. In September 2008, we met with the FDA to discuss the FDA s determination. The FDA asked us to provide a complete response to the not-approvable letter, which we submitted on November 6, 2008. The FDA accepted our complete response for review and has set a new target action date of May 6, 2009. There are no guarantees that the FDA will provide its response by May 6, 2009, nor can there be any assurances that any such response will be favorable. Pending the FDA s reply to our complete response, we have suspended all non-essential iloperidone-related activities.

Therapeutic opportunity

Schizophrenia is a chronic, debilitating mental disorder characterized by hallucinations, delusions, racing thoughts and other psychotic symptoms (collectively referred to as positive symptoms), as well as moodiness, anhedonia (inability to feel pleasure), loss of interest, eating disturbances and withdrawal (collectively referred to as negative symptoms), and additionally attention and memory deficits (collectively referred to as cognitive symptoms). Schizophrenia develops in late adolescence or early adulthood in approximately 1% of the world s population. Most schizophrenia patients today are treated with drugs known as atypical antipsychotics, which were first approved in the U.S. in the late 1980s. These antipsychotics have been named atypical for their ability to treat a broader range of negative symptoms than the first-generation typical antipsychotics, which were introduced in the 1950s and are now generic. Atypical antipsychotics are generally regarded as having improved side effect profiles and efficacy relative to typical antipsychotics and currently comprise approximately 90% of schizophrenia prescriptions. The global market for atypical antipsychotics was in excess of $20 billion in 2007, according to IMS. Currently approved atypical antipsychotics include olanzapine (Zyprexa®) by Eli Lilly and Company, risperidone (Risperdal®) and paliperidone

(Invega®), each by Ortho-McNeil-Janssen Pharmaceuticals, Inc., quetiapine (Seroquel®) by AstraZeneca, aripiprazole (Abilify®) by Bristol-Myers Squibb (BMS), ziprasidone (Geodon®) by Pfizer, and generic clozapine.

Limitations of current treatments

The treatment of schizophrenia remains challenging because currently approved antipsychotics, even atypical antipsychotics, often induce serious side effects and offer only modest and occasional efficacy. Side effects include weight gain, diabetes, extrapyramidal symptoms (involuntary bodily movements),

hyperprolactinemia (an elevated secretion of the hormone prolactin which can lead to sexual dysfunction and breast development and milk secretion in women and men), increased somnolence (sleepiness) and cognition difficulties. The side-effect profile and modest efficacy of currently available antipsychotics result in poor patient compliance with prescribed drug regimens. Consequently, there remains a high degree of dissatisfaction with atypical antipsychotics among physicians and patients. Research by LEK Consulting LLC (LEK Consulting), a leading consulting firm, supports this, showing that physicians employ a trial-and-error approach of prescribing a series of different atypical antipsychotics as they attempt to balance side effects and symptom management in each patient. In addition, the Clinical Antipsychotic Trials of Interventional Effectiveness (CATIE) study, conducted by the National Institute of Mental Health and reported in *The New England Journal of Medicine,* found that 74% of patients taking antipsychotics discontinued treatment within 18 months. The average time to discontinuation for these patients in the CATIE study was approximately 6 months.

Potential advantages of iloperidone

Iloperidone may offer several advantages over existing therapies. However, the definitive profile of the efficacy and safety of iloperidone will be determined by the final label approved by the FDA. Iloperidone is currently under review by the FDA for the treatment of schizophrenia, with a PDUFA target action date of May 6, 2009. Therefore, the following should not be considered a discussion of the definitive clinical profile of iloperidone.

Efficacy and safety. In a complete program of Phase II and Phase III trials comprising more than 3,000 patients, iloperidone showed efficacy equivalent to other atypical antipsychotics, as well as a reduced risk of the side effects most associated with atypical antipsychotics, including low weight gain, no induction of diabetes, low extrapyramidal symptoms, including no akathisia (inability to sit still), no hyperprolactinemia, low incidence of sleepiness and low negative effects on cognition relative to placebo. Like other atypical antipsychotics, iloperidone is associated with a prolongation of the heart s QTc interval, but in no instance did any patient taking iloperidone in the controlled portion of a clinical trial have an interval exceeding a 500-millisecond threshold that the FDA has identified as being of particular concern. Two patients experienced a prolongation of 500 milliseconds or more during the open-label extension of one trial. We believe that the safety profile of iloperidone may result in improved patient compliance with their treatment regimen.

Extended-release injectable formulation. Prior to our voluntary suspension of all nonessential iloperidone-related activities pending the FDA s reply to our complete response to the not-approvable letter, we were developing an extended-release injectable formulation for iloperidone, which is administered once every four weeks and which we believe will be a compelling complement to our oral formulation for both physicians and patients. Novartis conducted a two-month Phase I/IIa safety trial of this formulation in schizophrenia patients, in which it demonstrated the benefit of consistent release over a four-week time period with no greater side effects relative to oral dosing. If the FDA approves the oral formulation of iloperidone, we intend to resume the development of the injectable formulation and we believe we will need to conduct additional trials with this formulation to be able to file for FDA approval. The commercial potential for our extended-release injectable formulation has been demonstrated by the success of the injectable formulation for risperidone, Risperdal® Consta®, which achieved worldwide sales of approximately $1.1 billion in 2007, according to Alkermes Company press releases. We believe that our four-week formulation for iloperidone will be an attractive alternative to Risperdal® Consta®, which is required to be injected once every two weeks. Additionally, and unlike Risperdal® Consta®, we do not believe that the injectable formulation for iloperidone will require oral titration, which would result in simplified dosing.

Additionally, we plan to continue to apply our pharmacogenetics and pharmacogenomics expertise to develop tools that may allow physicians to avoid the trial-and-error approach to prescribing antipsychotic medications for their patients.

Pharmacogenetic evaluation of iloperidone s efficacy. Based on the results of our most recent Phase III trial, as well as analyses of prior clinical data for iloperidone, we have determined that certain patients

may be more likely to respond to iloperidone and to enjoy better treatment results relative to the general schizophrenia patient population. These patients have a common mutation of a gene, linked to central nervous system function, that is estimated to occur in approximately 70% of schizophrenia patients. We developed a genetic test which we used in our recently completed Phase III trial and confirmed this correlation. According to market research conducted by LEK Consulting, physicians treating schizophrenia patients would enthusiastically welcome a genetic test that would enable them to identify likely responders to iloperidone, given the unpredictable efficacy and serious side effects currently associated with atypical antipsychotics, and be more likely to prescribe iloperidone as a result.

Pharmacogenetic evaluation of iloperidone s safety. Based on the results of our most recent Phase III trial, and other pharmacogenetic analysis, we have discovered that patients with an uncommon mutation of a well understood gene affecting drug metabolism experience higher levels of iloperidone in their blood and may experience longer QTc intervals while taking iloperidone. We estimate that this genetic attribute is found in approximately 25-30% of schizophrenia patients, comprised of poor metabolizers (approximately 5-10% of schizophrenia patients) and intermediate metabolizers (approximately 20% of schizophrenia patients). We believe that certain physicians may choose to test patients for this mutation if they have a concern about QTc interval prolongation with respect to a particular patient.

Intellectual property

Iloperidone and its metabolites, formulations, genetic markers and uses are covered by a total of twenty-two patent and patent application families worldwide. The primary new chemical entity patent covering iloperidone expires normally in 2011 in the United States and 2010 in most of the major markets in Europe. In the United States, the United States Drug Price Competition and Patent Term Restoration act of 1984, more commonly known as the Hatch-Waxman Act provides for an extension of new chemical entity patents for a period of up to five years following the expiration of the patent covering that compound to compensate for time spent in development. We believe that iloperidone will qualify for the full five-year patent term extension. In Europe, similar legislative enactments provide for five-year extensions of new chemical entity patents through the granting of Supplementary Protection Certificates, and we believe that iloperidone will qualify for this extension as well. Consequently, assuming that we are granted all available extensions by the FDA and European regulatory authorities and that we receive regulatory approval, we expect that our rights to commercialize iloperidone will be exclusive until 2016 in the United States and until 2015 in Europe. Additionally, the patent application covering the depot formulation for iloperidone, if it is granted, will expire normally in 2022. Several other patent applications covering metabolites, uses, formulations and genetic markers relating to iloperidone extend beyond 2020. Pursuant to a European Union directive, we may also acquire market exclusivity (sometimes referred to as, data exclusivity) in most European Union countries for iloperidone for a period of 10 years from the date of its regulatory approval in Europe (with the possibility for a further one-year extension), even though the European patents covering iloperidone will likely expire prior to the end of such 10-year period. No generic versions of iloperidone would be permitted to be marketed or sold during this 10-year period in most European countries.

We acquired worldwide, exclusive rights to the new chemical entity patent covering iloperidone and certain related intellectual property from Novartis under a sublicense agreement we entered into in 2004. Please see License agreements below for a more complete description of the rights we acquired from Novartis with respect to iloperidone.

Tasimelteon

Tasimelteon is an oral compound in development for sleep and mood disorders, including Circadian Rhythm Sleep Disorders (CRSD). The compound binds selectively to the brain s melatonin receptors, which are thought to govern the

body s natural sleep/wake cycle. Compounds that bind selectively to these receptors are thought to be able to help treat sleep disorders, and additionally are believed to offer potential benefits in mood disorders. We announced positive top-line results from our Phase III trial of tasimelteon in transient insomnia in November 2006. In June 2008, the Company announced positive top-line results from the Phase III

trial of tasimelteon in chronic primary insomnia. Tasimelteon is also ready for Phase II trials for the treatment of depression.

Therapeutic opportunity

Industry sources estimate that of the 73 million U.S. adults who suffer from some form of insomnia, only approximately 11 million currently receive treatment. Sleep disorders are segmented into three major categories: primary insomnia, secondary insomnia and circadian rhythm sleep disorders. Insomnia is a symptom complex that comprises difficulty falling asleep or staying asleep, or non-refreshing sleep, in combination with daytime dysfunction or distress. The symptom complex can be an independent disorder (primary insomnia) or be a result of another condition such as depression or anxiety (secondary insomnia). Circadian rhythm sleep disorders result from a misalignment of the sleep/wake cycle and an individual s daily activities or lifestyle. The circadian rhythm is the rhythmic output of the human biological clock and is governed primarily by the hormone melatonin. Both the timing of behavioral events (activity, sleep, and social interactions) and the environmental light/dark cycle result in a sleep/wake cycle that follows the circadian rhythm. Examples of circadian rhythm sleep disorders include transient disorders such as jet lag and chronic disorders such as shift work sleep disorder. Market research we have conducted with LEK Consulting indicates that circadian rhythm sleep disorders represent a significant portion of the market for sleep disorders. In 2006, the sleep disorder drug market generated approximately $4.5 billion in worldwide sales, according to IMS.

There are a number of drugs approved and prescribed for patients with sleep disorders. The most commonly prescribed drugs are hypnotics, such as generic zolpidem, zolpidem tartrate (Ambien CR®, sanofi-aventis), eszopiclone (Lunesta®, Sepracor, Inc.) and zaleplon (Sonata®, King Pharmaceuticals, Inc.). Hypnotics work by acting upon a set of brain receptors known as GABA receptors, which are separate and distinct from the melatonin receptors to which tasimelteon binds. Several drugs in development, including indiplon (Neurocrine Biosciences), also utilize a mechanism of action involving binding to GABA receptors. Members of the benzodiazapine class of sedatives are also approved for insomnia, but their usage has declined due to an inferior safety profile compared to hypnotics. Anecdotal evidence also suggests that sedative antidepressants, such as trazodone and doxepin, are prescribed off-label for insomnia. The FDA approved drugs for treatment of insomnia also include ramelteon (Rozeremtm, Takeda Pharmaceuticals Company Limited), a compound with a mechanism of action similar to tasimelteon. There are no FDA-approved treatments for insomnia specifically related to Circadian Rhythm Sleep Disorders.

Limitations of current treatments

We believe that each of the drugs used to treat insomnia has inherent limitations that leave patients underserved. The key limitations include the potential for abuse, significant side effects, and a failure to address the underlying causes of sleeplessness:

Many of the products prescribed commonly for sleep disorders, including Ambien®, Lunesta®, and Sonata®, are classified as Schedule IV controlled substances by the United States Drug Enforcement Administration (DEA) due to their potential for abuse, tolerance and withdrawal symptoms. Drugs that are classified as Schedule IV controlled substances are subject to restrictions on how such drugs are prescribed and dispensed.

Many drugs approved for and used in sleep disorders also induce a number of nuisance side effects beyond the more serious abuse and addiction effects associated with most approved products. These side effects include next-day grogginess, memory loss, unpleasant taste, dry mouth and hormonal changes.

We believe that none of the drugs used and approved for sleep, other than Rozeremtm, work through the body s natural sleep/wake cycle, which is governed by melatonin. We believe that, for patients whose sleep disruption

is due to a misalignment of this sleep/wake cycle and these patients need to sleep (as is the case in circadian rhythm sleep disorders), a drug that naturally modulates the sleep/wake cycle would be an attractive new alternative because it would address the underlying cause of the sleeplessness, rather than merely addressing its symptoms.

Potential advantages of tasimelteon

We believe that tasimelteon may offer efficacy similar to the most efficacious of the approved sleep drugs, and that it may provide significant benefits to patients beyond those offered by the approved drugs. We believe that tasimelteon is unlikely to be scheduled as a controlled substance by the DEA because Rozeremtm, which has a similar mechanism of action to tasimelteon, was shown not to have potential for abuse and was not classified as a Schedule IV controlled substance by the DEA. However, despite the fact that the drugs have a similar mechanism of action, our Phase III results have demonstrated that tasimelteon may offer superior sleep maintenance to Rozeremtm. Tasimelteon also appears to be safe and well-tolerated, with no significant side effects or effects on next-day performance. For patients with circadian rhythm disorders, tasimelteon may be able to align the patient s sleep/wake cycle with his or her lifestyle, something we believe no approved sleep therapy has demonstrated. For example, in our Phase II trial of tasimelteon in transient insomnia with 37 healthy participants, tasimelteon induced a statistically significant ($p<0.025$) shift in circadian rhythm of up to five hours on the first night.

Overview of Phase III clinical trials

In November 2006, we reported positive top-line results in a randomized, double-blind, multi-center, placebo-controlled Phase III trial that enrolled 412 adults in a sleep laboratory setting using a phase-advance, first-night assessment model of induced transient insomnia. The trial examined tasimelteon dosed 30 minutes before bedtime at 20, 50 and 100 milligrams versus placebo.

Tasimelteon achieved significant results in multiple endpoints, demonstrating a benefit in both sleep onset, or time to fall asleep, and sleep maintenance, or ability to stay asleep. Based on these trial results, we believe that tasimelteon will compare favorably to efficacy achieved by currently approved insomnia drugs, not only for circadian rhythm sleep disorders but also for other types of insomnia. The Phase III trial also demonstrated that tasimelteon was safe and well-tolerated, with no significant side effects versus placebo and no impairment of next-day performance or mood.

In June 2008, we reported positive top-line results in a randomized, double-blind, placebo-controlled Phase III trail in chronic primary insomnia that enrolled 324 patients. The trial examined tasimelteon at 20 and 50 milligrams versus placebo over a period of 35 days. The trial measured time to fall asleep and sleep maintenance, as well as next-day performance. We will need to conduct additional Phase III trials of tasimelteon for the treatment of chronic sleep disorders to receive FDA approval of tasimelteon for the treatment of insomnia.

Potential indication for depression

We believe that tasimelteon may also be effective in treating depression. Agomelatine, another drug that acts on the brain s melatonin receptors, has demonstrated efficacy and safety in the treatment of depression that compared favorably to an approved antidepressant, Paxil® (paroxetine, GSK), in a Phase III trial. While the precise mechanism for the effect of drugs like tasimelteon, agomelatine and Rozeremtm, which act on the brain s melatonin receptors, is currently unknown, it is possible that, by improving sleep, these drugs could improve mood, since depressed patients are likely to have sleep disorders. It is also possible that mood disorders such as depression have an association with circadian rhythm misalignments.

Of the approximately 29 million adults in the United States who suffer from some form of depression, over 11 million are currently treated with a prescription antidepressant medication. Sales of antidepressants exceeded $19 billion globally in 2007, according to IMS.

We believe that tasimelteon will be differentiated from approved antidepressants in several ways. In the Phase III trial of agomelatine described above, agomelatine showed significantly improved mood in two weeks, versus four weeks for Paxil®. Consequently, tasimelteon may, with its similar properties to agomelatine, offer a more rapid onset of action than approved antidepressants. We believe that tasimelteon should also have an improved side effect profile when compared to approved products because we believe that it should not have the sexual side effects, weight gain, and sleep disruption associated with these products.

Tasimelteon is ready for Phase II trials in depression. It has demonstrated an antidepressant effect in animal models and has completed several Phase I trials, including one with four weeks of exposure, showing none of the serious side effects associated with the approved antidepressants.

Intellectual property

Tasimelteon and its formulations and uses are covered by a total of eleven patent and patent application families worldwide. The primary new chemical entity patent covering tasimelteon expires normally in 2017 in the United States and in most European markets. We believe that, like iloperidone, tasimelteon will meet the various criteria of the Hatch-Waxman Act and will receive five additional years of patent protection in the United States, which would extend its patent protection in the United States until 2022. In Europe, similar legislative enactments provide for five-year extensions of European new chemical entity patents through the granting of Supplementary Protection Certificates, and we believe that tasimelteon will qualify for such an extension, which would extend European patent protection for tasimelteon until 2022. Several other patent applications covering uses of tasimelteon will, if granted, provide exclusive rights for these uses until 2026. Our rights to the new chemical entity patent covering tasimelteon and related intellectual property have been acquired through a license with BMS. Please see License agreements below for a discussion of this license.

License agreements

Our rights to develop and commercialize our clinical-stage product candidates are subject to the terms and conditions of licenses granted to us by other pharmaceutical companies.

Iloperidone

We acquired exclusive worldwide rights to patents for iloperidone through a sublicense agreement with Novartis. A predecessor company of sanofi-aventis, Hoechst Marion Roussel, Inc. (HMRI), discovered iloperidone and completed early clinical work on the compound. In 1996, following a review of its product portfolio, HMRI licensed its rights to the iloperidone patents to Titan Pharmaceuticals, Inc. (Titan) on an exclusive basis. In 1997, soon after it had acquired its rights, Titan sublicensed its rights to iloperidone on an exclusive basis to Novartis. In June 2004, we acquired exclusive worldwide rights to these patents to develop and commercialize iloperidone through a sublicense agreement with Novartis. In partial consideration for this sublicense, we paid Novartis an initial license fee of $500,000 and are obligated to make future milestone payments to Novartis of less than $100 million in the aggregate (the majority of which are tied to sales milestones), as well as royalty payments to Novartis at a rate which, as a percentage of net sales, is in the mid-twenties. In November 2007, we met a milestone under this license agreement relating to the acceptance of our filing of the NDA for iloperidone for the treatment of schizophrenia and made a license payment of $5 million to Novartis.

Our rights with respect to the patents to develop and commercialize iloperidone may terminate, in whole or in part, if we fail to meet certain development or commercialization milestones relating to the time it takes for us to launch iloperidone commercially following regulatory approval, and the time it takes for us to receive regulatory approval following our submission of an NDA or equivalent foreign filing. Additionally, our rights may terminate in whole or in part if we do not meet certain other obligations under our sublicense agreement to make royalty and milestone payments, if we fail to comply with requirements in our sublicense agreement regarding our financial condition, or if we do not abide by certain restrictions in our sublicense agreement regarding other development activities.

Tasimelteon

In February 2004, we entered into a license agreement with BMS under which we received an exclusive worldwide license under certain patents and patent applications, and other licenses to intellectual property, to develop and commercialize tasimelteon. In partial consideration for the license, we paid BMS an initial license fee of $500,000. We are also obligated to make future milestone payments to BMS of less than $40 million in the aggregate (the majority of which are tied to sales milestones) as well as royalty payments based on the net

sales of tasimelteon at a rate which, as a percentage of net sales, is in the low teens. We made a milestone payment to BMS of $1,000,000 under this license agreement in 2006 relating to the initiation of our first Phase III clinical trial for tasimelteon. We are also obligated under this agreement to pay BMS a percentage of any sublicense fees, upfront payments and milestone and other payments (excluding royalties) that we receive from a third party in connection with any sublicensing arrangement, at a rate which is in the mid-twenties. We have agreed with BMS in our license agreement for tasimelteon to use our commercially reasonable efforts to develop and commercialize tasimelteon and to meet certain milestones in initiating and completing certain clinical work.

BMS holds certain rights with respect to tasimelteon in the license agreement. If we have not agreed to one or more partnering arrangements to develop and commercialize tasimelteon in certain significant markets with one or more third parties after the completion of the Phase III program, BMS has the option to exclusively develop and commercialize tasimelteon on its own on pre-determined financial terms, including milestone and royalty payments.

Either party may terminate the tasimelteon license agreement under certain circumstances, including a material breach of the agreement by the other. In the event that BMS has not exercised its option to reacquire the rights to tasimelteon and we terminate our license, or if BMS terminates our license due to our breach, all rights licensed and developed by us under this agreement will revert or otherwise be licensed back to BMS on an exclusive basis.

Government regulation

Government authorities in the United States, at the federal, state and local level, as well as foreign countries and local foreign governments, regulate the research, development, testing, manufacture, labeling, promotion, advertising, distribution, sampling, marketing, import and export of our product candidates. All of our products will require regulatory approval by government agencies prior to commercialization. In particular, human pharmaceutical products are subject to rigorous pre-clinical and clinical trials and other approval procedures of the FDA and similar regulatory authorities in foreign countries. The process of obtaining these approvals and the subsequent compliance with appropriate domestic and foreign laws, rules and regulations require the expenditure of significant time and human and financial resources.

United States government regulation

FDA approval process

In the United States, the FDA regulates drugs under the Federal Food, Drug and Cosmetic Act and implements regulations. If we fail to comply with the applicable requirements at any time during the product development process, approval process, or after approval, we may become subject to administrative or judicial sanctions. These sanctions could include the FDA s refusal to approve pending applications, withdrawals of approvals, clinical holds, warning letters, product recalls, product seizures, total or partial suspension of our operations, injunctions, fines, civil penalties or criminal prosecution. Any such sanction could have a material adverse effect on our business.

The steps required before a drug may be marketed in the United States include:

- pre-clinical laboratory tests, animal studies and formulation studies under Current Good Laboratory Practices (cGLP)

- submission to the FDA of an investigational new drug application, or IND, which must become effective before human clinical trials may begin

execution of adequate and well-controlled clinical trials to establish the safety and efficacy of the product for each indication for which approval is sought

submission to the FDA of an NDA

satisfactory completion of an FDA inspection of the manufacturing facility or facilities at which the product is produced to assess compliance with Current Good Manufacturing Practices (cGMP)

FDA review and approval of the NDA

Pre-clinical studies generally are conducted in laboratory animals to evaluate the potential safety and activity of a product. Violation of the FDA s cGLP regulations can, in some cases, lead to invalidation of the studies, requiring these studies to be replicated. In the United States, drug developers submit the results of pre-clinical trials, together with manufacturing information and analytical and stability data, to the FDA as part of the IND, which must become effective before clinical trials can begin in the United States. An IND becomes effective 30 days after receipt by the FDA unless before that time the FDA raises concerns or questions about issues such as the proposed clinical trials outlined in the IND. In that case, the IND sponsor and the FDA must resolve any outstanding FDA concerns or questions before clinical trials can proceed. If these concerns or questions are unresolved, the FDA may not allow the clinical trials to commence.

Pilot studies generally are conducted in a limited patient population, approximately three to 25 subjects, to determine whether the product candidate warrants further clinical trials based on preliminary indications of efficacy. These pilot studies may be performed in the United States after an IND has become effective or outside of the United States prior to the filing of an IND in the United States in accordance with government regulations and institutional procedures.

Clinical trials involve the administration of the investigational product candidate to human subjects under the supervision of qualified investigators. Clinical trials are conducted under protocols detailing, among other things, the objectives of the study, the parameters to be used in assessing the safety and the effectiveness of the drug. Each protocol must be submitted to the FDA as part of the IND prior to beginning the trial.

Typically, clinical evaluation involves a time-consuming and costly three-Phase sequential process, but the phases may overlap. Each trial must be reviewed, approved and conducted under the auspices of an independent Institutional Review Board, and each trial must include the patient s informed consent.

Phase I: refers typically to closely-monitored clinical trials and includes the initial introduction of an investigational new drug into human patients or health volunteer subjects. Phase I trials are designed to determine the safety, metabolism and pharmacologic actions of a drug in humans, the potential side effects associated with increasing drug doses and, if possible, to gain early evidence of the product candidate s effectiveness. Phase I trials also include the study of structure-activity relationships and mechanism of action in humans, as well as studies in which investigational drugs are used as research tools to explore biological phenomena or disease processes. During Phase I trials, sufficient information about a drug s pharmacokinetics and pharmacological effects should be obtained to permit the design of well-controlled, scientifically valid Phase II studies. The total number of subjects and patients included in Phase I trials varies, but is generally in the range of 20 to 80 people.

Phase II: refers to controlled clinical trials conducted to evaluate appropriate dosage and the effectiveness of a drug for a particular indication or indications in patients with a disease or condition under study and to determine the common short-term side effects and risks associated with the drug. These trials are typically well-controlled, closely monitored and conducted in a relatively small number of patients, usually involving no more than several hundred subjects.

Phase III: refers to expanded controlled and uncontrolled clinical trials. These trials are performed after preliminary evidence suggesting effectiveness of a drug has been obtained. Phase III trials are intended to

gather additional information about the effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug and to provide an adequate basis for physician labeling. Phase III trials usually include several hundred to several thousand subjects.

Phase I, II and III testing may not be completed successfully within any specified time period, if at all. The FDA closely monitors the progress of each of the three phases of clinical trials that are conducted in the United States and may, at its discretion, reevaluate, alter, suspend or terminate the testing based upon the data accumulated to that point and the FDA s assessment of the risk/benefit ratio to the patient. A clinical program

is designed after assessing the causes of the disease, the mechanism of action of the active pharmaceutical ingredient of the product candidate and all clinical and pre-clinical data of previous trials performed. Typically, the trial design protocols and efficacy endpoints are established in consultation with the FDA. Upon request through a special protocol assessment, the FDA can also provide specific guidance on the acceptability of protocol design for clinical trials. The FDA or we may suspend or terminate clinical trials at any time for various reasons, including a finding that the subjects or patients are being exposed to an unacceptable health risk. The FDA can also request additional clinical trials be conducted as a condition to product approval. During all clinical trials, physicians monitor the patients to determine effectiveness and to observe and report any reactions or other safety risks that may result from use of the drug candidate.

Assuming successful completion of the required clinical trials, drug developers submit the results of pre-clinical studies and clinical trials, together with other detailed information including information on the manufacture and composition of the product, to the FDA, in the form of an NDA, requesting approval to market the product for one or more indications. In most cases, the NDA must be accompanied by a substantial user fee. The FDA reviews an NDA to determine, among other things, whether a product is safe and effective for its intended use.

Before approving an NDA, the FDA will inspect the facility or facilities where the product is manufactured. The FDA will not approve the application unless cGMP compliance is satisfactory. The FDA will issue an approval letter if it determines that the application, manufacturing process and manufacturing facilities are acceptable. If the FDA determines that the NDA, manufacturing process or manufacturing facilities are not acceptable, it will outline the deficiencies in the submission and will often request additional testing or information. Notwithstanding the submission of any requested additional information, the FDA may ultimately decide that the NDA does not satisfy the regulatory criteria for approval and refuse to approve the NDA by issuing a not approvable letter which is not subsequently withdrawn or reversed by the FDA.

The testing and approval process requires substantial time, effort and financial resources, and each may take several years to complete. The FDA may not grant approval on a timely basis, or at all. We may encounter difficulties or unanticipated costs in our efforts to secure necessary governmental approvals, which could delay or preclude us from marketing our products. Furthermore, the FDA may prevent a drug developer from marketing a product under a label for its desired indications or place other conditions on distribution as a condition of any approvals, which may impair commercialization of the product. After approval, some types of changes to the approved product, such as adding new indications, manufacturing changes and additional labeling claims, are subject to further FDA review and approval. Similar regulatory procedures must also be complied with in countries outside the United States.

If the FDA approves the new drug application, the drug becomes available for physicians to prescribe in the United States. After approval, we will have to comply with a number of post-approval requirements, including delivering periodic reports to the FDA, submitting descriptions of any adverse reactions reported, and complying with drug sampling and distribution requirements. We will also be required to provide updated safety and efficacy information and to comply with requirements concerning advertising and promotional labeling. Also, our quality control and manufacturing procedures must continue to conform to cGMP after approval. Drug manufacturers and their subcontractors are required to register their facilities and are subject to periodic unannounced inspections by the FDA to assess compliance with cGMP which imposes certain procedural and documentation requirements relating to quality assurance and quality control. Accordingly, manufacturers must continue to expend time, money and effort in the area of production and quality control to maintain compliance with cGMP and other aspects of regulatory compliance. The FDA may require post market testing and surveillance to monitor the product s safety or efficacy, including additional studies, known as Phase IV trials, to evaluate long-term effects.

In addition to studies requested by the FDA after approval, we may have to conduct other trials and studies to explore use of the approved compound for treatment of new indications, which require FDA approval. The purpose of these

trials and studies is to broaden the application and use of the drug and its acceptance in the medical community.

We use, and will continue to use, third-party manufacturers to produce our products in clinical and commercial quantities. Future FDA inspections may identify compliance issues at our facilities or at the facilities of our contract manufacturers that may disrupt production or distribution, or require substantial resources to correct. In addition, discovery of problems with a product or the failure to comply with requirements may result in restrictions on a product, manufacturer or holder of an approved NDA, including withdrawal or recall of the product from the market or other voluntary or FDA-initiated action that could delay further marketing. Newly discovered or developed safety or effectiveness data may require changes to a product s approved labeling, including the addition of new warnings and contraindications.

On September 27, 2007, the Food and Drug Administration Amendments Act, or the FDAAA, was enacted into law, amending both the FDC Act and the Public Health Service Act. The FDAAA makes a number of substantive and incremental changes to the review and approval processes in ways that could make it more difficult or costly to obtain approval for new pharmaceutical products, or to produce, market and distribute existing pharmaceutical products. Most significantly, the law changes the FDA s handling of postmarked drug product safety issues by giving the FDA authority to require post approval studies or clinical trials, to request that safety information be provided in labeling, or to require an NDA applicant to submit and execute a Risk Evaluation and Mitigation Strategy, or REMS.

The FDAAA also reauthorized the authority of the FDA to collect user fees to fund the FDA s review activities and made certain changes to the user fee provisions to permit the use of user fee revenue to fund FDA s drug safety activities and the review of Direct-to-Consumer advertisements.

In addition, new government requirements may be established that could delay or prevent regulatory approval of our products under development.

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 FDA s 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 FDA cannot grant effective approval of an ANDA based on that listed drug.

Foreign regulation

Whether or not we obtain FDA approval for a product, we must obtain approval of a product by the comparable regulatory authorities of foreign countries before we can commence clinical trials or marketing of the product in those countries. The approval process varies from country to country, and the time may be longer or shorter than that required for FDA approval. The requirements governing the conduct of clinical trials, product licensing, pricing and reimbursement also vary greatly from country to country. Although governed by the applicable country, clinical trials conducted outside of the United States typically are administered with the three-Phase sequential process that is discussed above under United States government regulation. However, the foreign equivalent of an IND is not a prerequisite to performing pilot studies or Phase I clinical trials.

Under European Union regulatory systems, we may submit marketing authorization applications either under a centralized or decentralized procedure. The centralized procedure, which is available for products produced by biotechnology or which are highly innovative, provides for the grant of a single marketing authorization that is valid for all European Union member states. This authorization is a marketing authorization approval. The decentralized procedure provides for mutual recognition of national approval decisions. Under this procedure, the holder of a national marketing authorization may submit an application to the remaining member states. Within 90 days of receiving the applications and assessment report, each member state must decide whether to recognize approval. This procedure is referred to as the mutual recognition procedure.

In addition, regulatory approval of prices is required in most countries other than the United States. We face the risk that the resulting prices would be insufficient to generate an acceptable return to us or our collaborators.

Third-party reimbursement and pricing controls

In the United States and elsewhere, sales of pharmaceutical products depend in significant part on the availability of reimbursement to the consumer from third-party payors, such as government and private insurance plans. Third-party payors are increasingly challenging the prices charged for medical products and services. It will be time consuming and expensive for us to go through the process of seeking reimbursement from Medicare and private payors. Our products may not be considered cost-effective, and coverage and reimbursement may not be available or sufficient to allow us to sell our products on a competitive and profitable basis. The passage of the Medicare Prescription Drug and Modernization Act of 2003 imposes new requirements for the distribution and pricing of prescription drugs which may affect the marketing of our products.

In many foreign markets, including the countries in the European Union and Japan, pricing of pharmaceutical products is subject to governmental control. In the United States, there have been, and we expect that there will continue to be, a number of federal and state proposals to implement similar governmental pricing control. While we cannot predict whether such legislative or regulatory proposals will be adopted, the adoption of such proposals could have a material adverse effect on our business, financial condition and profitability.

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Marketing and sales

We have suspended all pre-launch commercial activities relating to iloperidone pending the outcome of the FDA s review of our complete response. We are uncertain at this time when or if we expect to start marketing iloperidone commercially. The time it takes to receive cash inflows from the sale of iloperidone is highly dependent on facts and circumstances that we may not be able to control and are subject to a number of risks. We currently have limited sales, marketing or distribution capabilities and do not plan to continue to develop these capabilities internally, or enter into partnering arrangements to the extent that we believe large sales and marketing forces will be necessary at this time. However, because we believe that the number of physicians that would generate the majority of prescriptions for iloperidone in the United States is relatively small, we believe that we can cost-effectively develop our own sales force to market and sell iloperidone in the United States. We intend to seek commercial partners for iloperidone outside the United States and, even if we are able to develop our own sales force to market and sell iloperidone in the United States, we may decide to commercialize iloperidone in the United States with a partner, rather than on our own. In addition, given the range of potential indications for tasimelteon, we intend to pursue one or more partnerships for the development and commercialization of tasimelteon worldwide.

Patents and proprietary rights; Hatch-Waxman protection

We will be able to protect our products from unauthorized use by third parties only to the extent that our products are covered by valid and enforceable patents, either licensed in from third parties or generated internally, that give us sufficient proprietary rights. Accordingly, patents and other proprietary rights are essential elements of our business.

Our two current compounds in clinical development are covered by new chemical entity and other patents. These patents cover the active portions of our compounds and provide patent protection for all formulations containing these active portions. The new chemical entity patent for iloperidone is owned by sanofi-aventis, and other patents and patent applications relating to iloperidone are owned by Novartis. BMS owns the new chemical entity patent for tasimelteon. For both compounds we have obtained exclusive worldwide rights to develop and commercialize the compounds covered by these patents through license and sublicense arrangements. For more on these license and sublicense arrangements, please see License agreements above. In addition, we have generated intellectual property, and filed patent applications covering this intellectual property, for each of the compounds.

The new chemical entity patent covering iloperidone expires normally in 2011 in the United States and in 2010 in most European markets. The new chemical entity patent covering tasimelteon expires in 2017 in the United States and most European markets. Additionally, for each of our late-stage compounds, an additional period of exclusivity in the United States of up to five years following the expiration of the patent covering that compound may be obtained pursuant to the Hatch-Waxman Act. Assuming we gain such a five-year extension and that we continue to have our intellectual property rights under our sublicense and license agreements, we would have exclusive new chemical entity patent rights in the U.S. for iloperidone until 2016 and for tasimelteon until 2022. In Europe, similar legislative enactments may allow us to obtain five-year extensions of the European new chemical entity patents covering our product candidates through the granting of Supplementary Protection Certificates, which would allow us to have exclusive European new chemical entity patent rights for iloperidone until 2015 and for tasimelteon until 2022. Additionally, a directive in the European Union allows companies who receive European regulatory approval for a new compound to have a 10-year period of market exclusivity in most European countries for that compound (with the possibility of a further one-year extension), beginning on the date of such European regulatory approval, regardless of when the European new chemical entity patent covering such compound expires. No generic version of an approved drug may be marketed or sold in most European countries during this 10-year period. This directive may be of particular importance with respect to iloperidone, since the European new chemical entity patent for iloperidone will likely expire prior to the end of this 10-year period of market exclusivity.

Aside from the new chemical entity patents covering our current late-stage compounds, as of December 31, 2008 we had twenty-two pending provisional patent applications in the United States, five U.S. national

stage applications under U.S.C. 371 and five pending Patent Cooperation Treaty applications. The claims in these various patents and patent applications are directed to compositions of matter, including claims covering other product candidates, pharmaceutical compositions, genetic markers, and methods of use.

For proprietary know-how that is not appropriate for patent protection, processes for which patents are difficult to enforce and any other elements of our discovery process that involve proprietary know-how and technology that is not covered by patent applications, we rely on trade secret protection and confidentiality agreements to protect our interests. We require all of our employees, consultants and advisors to enter into confidentiality agreements. Where it is necessary to share our proprietary information or data with outside parties, our policy is to make available only that information and data required to accomplish the desired purpose and only pursuant to a duty of confidentiality on the part of those parties.

Manufacturing

We currently depend and expect to continue to depend on a small number of third-party manufacturers to produce sufficient quantities of our product candidates for use in our clinical studies. We are not obligated to obtain our product candidates from any particular third-party manufacturer and we believe that we would be able to obtain our product candidates from a number of third-party manufacturers at comparable cost.

If any of our product candidates are approved for commercial use, we plan to rely on third-party contract manufacturers to produce sufficient quantities for large-scale commercialization. If we do enter into commercial manufacturing arrangements with third parties, these third-party manufacturers will be subject to extensive governmental regulation. Specifically, regulatory authorities in the markets which we intend to serve will require that drugs be manufactured, packaged and labeled in conformity with cGMP or equivalent foreign standards. We intend to engage only those contract manufacturers who have the capability to manufacture drug products in compliance with cGMP and other applicable standards in bulk quantities for commercial use.

Competition

The pharmaceutical industry and the central nervous system segment of that industry, in particular, is highly competitive and includes a number of established large and mid-sized companies with greater financial, technical and personnel resources than we have and significantly greater commercial infrastructures than we have. Our market segment also includes several smaller emerging companies whose activities are directly focused on our target markets and areas of expertise. If approved, our product candidates will compete with numerous therapeutic treatments offered by these competitors. While we believe that our product candidates will have certain favorable features, existing and new treatments may also possess advantages. Additionally, the development of other drug technologies and methods of disease prevention are occurring at a rapid pace. These developments may render our product candidates or technologies obsolete or noncompetitive.

We believe the primary competitors for each of our product candidates are as follows:

- For iloperidone in the treatment of schizophrenia, the atypical antipsychotics Risperdal® (risperidone), including the depot formulation Risperdal® Consta®, and Invega® (paliperidone), each by Ortho-McNeil-Janssen Pharmaceuticals, Inc., Zyprexa® (olanzapine) by Eli Lilly and Company, Seroquel® (quetiapine) by AstraZeneca PLC, Abilify® (aripiprazole) by BMS/Otsuka Pharmaceutical Co., Ltd., Geodon® (ziprasidone) by Pfizer Inc., and generic clozapine, as well as the typical antipsychotics haloperidol, chlorpromazine, thioridazine, and sulpiride (all of which are generic). In addition to the approved products, compounds in Phase III trials (or for which an NDA has been recently filed) for the treatment of schizophrenia include bifeprunox (Solvay S.A./Lundbeck A/S), and asenapine (Schering-Plough Corporation) and

pimavanserin (Acadia Pharmaceuticals).

For tasimelteon in the treatment of insomnia, Rozerem™ (ramelteon) by Takeda Pharmaceuticals Company Limited, hypnotics such as Ambien® (zolpidem) by sanofi-aventis (including Ambien CR®), Lunesta® (eszopiclone) by Sepracor Inc. and Sonata® (zaleplon) by King Pharmaceuticals, Inc., generic compounds such as zolpidem, trazodone and doxepin, and over-the-counter remedies such as Benadryl® and Tylenol PM®. In addition to the approved products, compounds in Phase III trials for insomnia (or

for which an NDA has been recently filed) include indiplon (Neurocrine Biosciences, Inc.) and low-dose doxepin (Silenor™) by Somaxon Pharmaceuticals, Inc.

For tasimelteon in the treatment of depression, antidepressants such as Paxil® (paroxetine) by GlaxoSmithKline (GSK), Zoloft® (sertraline) by Pfizer, Prozac® (fluoxetine) by Eli Lilly, Lexapro (escitalopram) by Lundbeck A/S /Forest Pharmaceuticals Inc., and Effexor® (venlafaxine) by Wyeth as well as other compounds such as Wellbutrin® (buproprion) by GSK, Cymbalta® (duloxetine) by Eli Lilly, and Valdoxan (agomelatine) by Novartis and Les Laboratories Servier.

Our ability to compete successfully will depend in part on our ability to utilize our pharmacogenetics and pharmacogenomics and drug development expertise to identify, develop, secure rights to and obtain regulatory approvals for promising pharmaceutical compounds before others are able to develop competitive products. Our ability to compete successfully will also depend on our ability to attract and retain skilled and experienced personnel. Additionally, our ability to compete may be affected because insurers and other third-party payors in some cases seek to encourage the use of cheaper, generic products, which could make our products less attractive.

Employees

On December 16, 2008, we committed to a plan of termination that resulted in a work force reduction of 17 employees, including two officers, in order to reduce operating costs. We commenced notification of employees affected by the workforce reduction on December 17, 2008. As of December 31, 2008, we employed 24 full-time employees. This represents approximately a 55% decrease from the 53 employees we had on August 1, 2008.

Of the 24 full-time employees we had as of December 31, 2008, 15 were primarily engaged in research and development activities. None of our employees are represented by a labor union. We have not experienced any work stoppages and consider our employee relations to be good.

Corporate information

We were incorporated in Delaware in 2002. Our principal executive offices are located at 9605 Medical Center Drive, Suite 300, Rockville, Maryland, 20850 and our telephone number is (240) 599-4500. Our website address is www.vandapharma.com.

Available Information

Vanda Pharmaceuticals Inc. files annual, quarterly, and current reports, proxy statements, and other documents with the Securities and Exchange Commission (SEC) under the Securities Exchange Act of 1934 (the Exchange Act). The public may read and copy any materials that we file 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. Also, the SEC maintains an Internet website that contains reports, proxy and information statements, and other information regarding issuers, including us, that file electronically with the SEC. The public can obtain any documents that we file with the SEC at www.sec.gov.

We also make available free of charge on our Internet website at www.vandapharma.com our annual reports on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K, and, if applicable, amendments to those reports filed or furnished pursuant to Section 13(a) or 15(d) of the Exchange Act as soon as reasonably practicable after we electronically file such material with, or furnish it to, the SEC.

Our code of ethics, other corporate policies and procedures, and the charters of our Audit Committee, Compensation Committee and Nominating/Corporate Governance Committee are available through our Internet website at www.vandapharma.com.

ITEM 1A. RISK FACTORS

Investing in our common stock involves a high degree of risk. You should consider carefully the risks and uncertainties described below, together with all of the other information in this report, including the consolidated financial statements and the related notes appearing at the end of this annual report on Form 10-K/A, with respect to any investment in shares of our common stock. If any of the following risks actually occurs, our business, financial condition, results of operations and future prospects would likely be materially and adversely affected. In that event, the market price of our common stock could decline and you could lose all or part of your investment.

Risks related to our business and industry

If we fail to obtain approval for and commercialize our most advanced product candidate, iloperidone, we may have to curtail our product development programs and our business would be materially harmed.

We have invested a significant portion of our time, financial resources and collaboration efforts in the development of our most advanced product candidate, iloperidone, a compound for the treatment of schizophrenia. Our near-term ability to generate revenues and our future success, in large part, depends on the development and commercialization of iloperidone.

In November 2007, we announced that the FDA had accepted our New Drug Application (NDA) for iloperidone in schizophrenia. On July 25, 2008, we received a letter from the FDA stating that our NDA for iloperidone in schizophrenia was not approvable. The FDA indicated that it would require an additional clinical trial comparing iloperidone to placebo and including an active comparator such as olanzapine (Zyprexa®, Eli Lilly and Company) or risperidone (Risperdal®, Ortho-McNeil-Janssen Pharmaceuticals, Inc.) in patients with schizophrenia to further demonstrate the compound s efficacy. The FDA also stated that it would require us to obtain additional safety data for patients at a dose range of 20 to 24 mg/day of iloperidone. On September 10, 2008, we met with the FDA to discuss the FDA s position. The FDA asked us to provide a complete response to the not-approvable letter, which we submitted on November 6, 2008. The FDA accepted the complete response for review and has set a new target action date of May 6, 2009. If we are unable to satisfactorily demonstrate efficacy compared to placebo as well as an active comparator, if the FDA disagrees with our characterization approach or does not agree that we have demonstrated adequate efficacy for iloperidone, if we fail to resolve questions raised in the FDA s correspondence regarding the iloperidone NDA or if we otherwise fail to meet FDA requirements for the NDA or obtain FDA approval for, and successfully commercialize, iloperidone, we may never realize revenue from this product and we may have to curtail our other product development programs. As a result, our business would be materially harmed.

Our success is dependent on the success of our two product candidates in clinical development: iloperidone and tasimelteon. If either of these product candidates is determined to be unsafe or ineffective in humans, whether in clinical trials or commercially, our business will be materially harmed.

Despite the positive results of our completed trials, we are uncertain whether either of our current product candidates in clinical development will ultimately prove to be effective and safe in humans. Frequently, product candidates that have shown promising results in clinical trials have suffered significant setbacks in later clinical trials or even after they are approved for commercial sale. Future uses of any of our product candidates, whether in clinical trials or commercially, may reveal that the product candidate is ineffective, unacceptably toxic, has other undesirable side effects or is otherwise not fit for further use. If we are unable to discover and develop products that are safe and effective, our business will be materially harmed.

Any failure or delay in completing clinical trials for our product candidates could severely harm our business.

Pre-clinical studies and clinical trials required to demonstrate the safety and efficacy of our product candidates are time-consuming and expensive and together take several years to complete. The completion of clinical trials for our product candidates may be delayed by many factors, including:

- our inability to manufacture or obtain from third parties materials sufficient for use in pre-clinical studies and clinical trials
- delays in patient enrollment and variability in the number and types of patients available for clinical trials
- difficulty in maintaining contact with patients after treatment, resulting in incomplete data
- poor effectiveness of product candidates during clinical trials
- unforeseen safety issues or side effects
- governmental or regulatory delays and changes in regulatory requirements and guidelines

If we fail to complete successfully one or more clinical trials for either of our product candidates, we may not receive the regulatory approvals needed to market that product candidate. Therefore, any failure or delay in commencing or completing these clinical trials would harm our business materially.

We face heavy government regulation, and FDA regulatory approval of our products is uncertain.

The research, testing, manufacturing and marketing of drug products such as those that we are developing are subject to extensive regulation by federal, state and local government authorities, including the FDA. To obtain regulatory approval of a product, we must demonstrate to the satisfaction of the applicable regulatory agency that, among other things, the product is safe and effective for its intended use. In addition, we must show that the manufacturing facilities used to produce the products are in compliance with current Good Manufacturing Practices regulations or cGMP.

The process of obtaining FDA and other required regulatory approvals and clearances will require us to expend substantial time and capital. Despite the time and expense expended, regulatory approval is never guaranteed. The number of pre-clinical and clinical trials that will be required for FDA approval varies depending on the drug candidate, the disease or condition that the drug candidate is in development for, and the requirements applicable to that particular drug candidate. The FDA can delay, limit or deny approval of a drug candidate for many reasons, including that:

- a drug candidate may not be shown to be safe or effective
- the FDA may interpret data from pre-clinical and clinical trials in different ways than we do
- the FDA may not approve our manufacturing process
- the FDA may change their approval policies or adopt new regulations
- the FDA may not meet, or may extend, the PDUFA date with respect to a particular NDA

For example, if certain of our methods for analyzing our trial data are not accepted by the FDA, we may fail to obtain regulatory approval for our product candidates.

Moreover, if and when our products do obtain marketing approval, the marketing, distribution and manufacture of such products would remain subject to extensive ongoing regulatory requirements. Failure to comply with applicable regulatory requirements could result in:

warning letters

fines

civil penalties

injunctions

recall or seizure of products

total or partial suspension of production

refusal of the government to grant future approvals

withdrawal of approvals

criminal prosecution

Any delay or failure by us to obtain regulatory approvals for our product candidates could diminish competitive advantages that we may attain and would adversely affect the marketing of our products. We have not received regulatory approval to market any of our product candidates in any jurisdiction.

In November 2007, we announced that the FDA had accepted the NDA for iloperidone in schizophrenia. In July 2008, we announced that the FDA had determined that our NDA was not approvable and indicated, among other things, that we would have to conduct additional studies and submit that data before the FDA would approve iloperidone for commercial sale for the treatment of schizophrenia. Performance and completion of additional clinical studies will require years of testing and, even if positive results are achieved, may not result in the FDA s approval of iloperidone. In September 2008, we met with the FDA to discuss the FDA s determination. The FDA asked us to provide a complete response to the not-approvable letter, which we submitted on November 6, 2008. The FDA has accepted the complete response for review and has set a new target action date of May 6, 2009. We have no assurances that the response we receive from the FDA will be favorable. An unfavorable response may have a materially harmful effect on our business.

Even if we do receive regulatory approval for our drug candidates, the FDA may impose limitations on the indicated uses for which our products may be marketed, subsequently withdraw approval or take other actions against us or our products that are adverse to our business. The FDA generally approves products for particular indications. An approval for a more limited indication reduces the size of the potential market for the product. Product approvals, once granted, may be withdrawn if problems occur after initial marketing.

We also are subject to numerous federal, state and local laws, regulations and recommendations relating to safe working conditions, laboratory and manufacturing practices, the environment and the use and disposal of hazardous substances used in connection with our discovery, research and development work. In addition, we cannot predict the extent of government regulations or the impact of new governmental regulations that might significantly harm the discovery, development, production and marketing of our products. We may be required to incur significant costs to comply with current or future laws or regulations, and we may be adversely affected by the cost of such compliance.

We intend to seek regulatory approvals for our products in foreign jurisdictions, but we may not obtain any such approvals.

We intend to market our products outside the United States with one or more commercial partners. In order to market our products in foreign jurisdictions, we may be required to obtain separate regulatory approvals and to comply with numerous and varying regulatory requirements. The approval procedure varies among countries and jurisdictions and can involve additional trials, and the time required to obtain approval may differ from that required to obtain FDA approval. We have no experience with obtaining any such foreign approvals. Additionally, the foreign regulatory

approval process may include all of the risks associated with obtaining FDA approval. For all of these reasons, we may not obtain foreign regulatory approvals on a timely basis, if at all. Approval by the FDA does not ensure approval by regulatory authorities in other countries or jurisdictions, and approval by one foreign regulatory authority does not ensure approval by regulatory authorities in other foreign countries or jurisdictions or by the FDA. We may not be able to file for regulatory approvals and may not receive necessary approvals to commercialize our products in any market. The failure to obtain these approvals could harm our business materially.

Our product candidates may cause undesirable side effects or have other properties that could delay or prevent their regulatory approval or limit their marketability.

Undesirable side effects caused by our product candidates could interrupt, delay or halt clinical trials and could result in the denial of regulatory approval by the FDA or other regulatory authorities for any or all targeted indications, and in turn prevent us from commercializing our product candidates and generating revenues from their sale. For example, like many other drugs in its class, iloperidone is associated with a prolongation of the heart s QTc interval, which is a measurement of specific electrical activity in the heart as captured on an electrocardiogram, corrected for heart rate. A QTc interval that is significantly prolonged may result in an abnormal heart rhythm with adverse consequences including fainting, dizziness, loss of consciousness and death. No patient in the controlled portion of any of iloperidone s clinical trials was observed to have an interval that exceeded a 500-millisecond threshold of particular concern to the FDA. Two patients experienced a prolongation of 500 milliseconds or more during the open-label extension of one trial. We will continue to assess the side effect profile of iloperidone and our other product candidates in our ongoing clinical development program.

In addition, if any of our product candidates receive marketing approval and we or others later identify undesirable side effects caused by the product, we could face one or more of the following:

- regulatory authorities may require the addition of labeling statements, such as a black box warning or a contraindication
- regulatory authorities may withdraw their approval of the product
- we may be required to change the way the product is administered, conduct additional clinical trials or change the labeling of the product
- our reputation may suffer

Any of these events could prevent us from achieving or maintaining market acceptance of the affected product or could substantially increase the costs and expenses of commercializing the product candidate, which in turn could delay or prevent us from generating significant revenues from its sale.

Our product candidates may never achieve market acceptance even if we obtain regulatory approvals.

Even if we receive regulatory approvals for the sale of our product candidates, the commercial success of these products will depend, among other things, on their acceptance by physicians, patients, third-party payors and other members of the medical community as a therapeutic and cost-effective alternative to competing products and treatments. The degree of market acceptance of any of our product candidates will depend on a number of factors, including the demonstration of its safety and efficacy, its cost-effectiveness, its potential advantages over other therapies, the reimbursement policies of government and third-party payors with respect to the product candidate, and the effectiveness of our marketing and distribution capabilities. If our product candidates fail to gain market acceptance, we may be unable to earn sufficient revenue to continue our business. If our product candidates do not become widely accepted by physicians, patients, third-party payors and other members of the medical community, it is unlikely that we will ever become profitable.

If we fail to obtain the capital necessary to fund our research and development activities and commercialization efforts, we may be unable to continue operations or we may be forced to share our rights to commercialize our product candidates with third parties on terms that may not be attractive to us.

Our activities will necessitate significant uses of working capital for the foreseeable future. Our capital requirements will depend on many factors, including the success of our research and development efforts, the satisfaction of certain regulatory requirements, payments received under contractual agreements with other parties, if any, and the status of competitive products. However, given the recent decision by the FDA with respect to the NDA for iloperidone, and that any additional study or studies required by the FDA in order to obtain approval of iloperidone would require significant capital in excess of our currently available resources, we are now operating under a reduced spending plan and believe that, if we continue to operate under our

reduced spending plan, our existing cash, cash equivalents and marketable securities will be sufficient to fund operations at least through 2010. In budgeting for our activities, we have relied on a number of assumptions, including assumptions that we will not conduct any additional clinical trials for either of the oral or injectable formulations of iloperidone, that we will not engage in any further commercial activities related to iloperidone, that we will not engage in further in-licensing activities, that we will not receive any proceeds from potential partnerships, that we will not conduct additional trials for tasimelteon, that we will be able to retain our key personnel, that we will continue to seek FDA approval of iloperidone, that we will continue to evaluate clinical and pre-clinical compounds for potential development, and that we will not incur any significant contingent liabilities.

We may need to raise additional funds if one or more of our assumptions proves to be incorrect or if we choose to resume our commercialization efforts with respect to iloperidone, expand our product development efforts, conduct additional clinical trials for one or more of our product candidates or seek to acquire additional product candidates, and we may decide to raise additional funds even before they are needed if the conditions for raising capital are favorable. In our capital-raising efforts, we may seek to sell additional equity or debt securities or obtain a bank credit facility. The sale of additional equity or debt securities, if convertible, could result in dilution to our stockholders. The incurrence of indebtedness would result in increased fixed obligations and could also result in covenants that would restrict our operations. However, we may not be able to raise additional funds on acceptable terms, or at all. Given the current global economic climate, we may have more difficulty raising funds than we would during a period of economic stability. If we are unable to secure sufficient capital to fund our research and development activities, we may not be able to continue operations, or we may have to enter into collaboration agreements that could require us to share commercial rights to our products to a greater extent or at earlier stages in the drug development process than is currently intended. These collaborations, if consummated prior to proof-of-efficacy or safety of a given product candidate, could impair our ability to realize value from that product candidate.

We have incurred operating losses in each year since our inception and expect to continue to incur substantial and increasing losses for the foreseeable future.

We have a limited operating history. We have not generated any revenue from product sales to date and we cannot estimate with precision the extent of our future losses. We do not currently have any products that have been approved for commercial sale and we may never generate revenue from selling products or achieve profitability. We expect to continue to incur substantial and increasing losses for the foreseeable future, particularly if we receive FDA approval of our iloperidone NDA and resume commercial planning and activities or we otherwise increase our research, clinical development and administrative activities. As a result, we are uncertain when or if we will achieve profitability and, if so, whether we will be able to sustain it. We have been engaged in identifying and developing compounds and product candidates since March 2003. As of December 31, 2008, we have accumulated net losses of approximately $225.0 million. Our ability to achieve revenue and profitability is dependent on our ability to complete the development of our product candidates, obtain necessary regulatory approvals, and have our products manufactured and marketed. We cannot assure you that we will be profitable even if we successfully commercialize our products. Failure to become and remain profitable may adversely affect the market price of our common stock and our ability to raise capital and continue operations.

If our contract research organizations do not successfully carry out their duties or if we lose our relationships with contract research organizations, our drug development efforts could be delayed.

We are dependent on contract research organizations, third-party vendors and investigators for pre-clinical testing and clinical trials related to our drug discovery and development efforts and we will likely continue to depend on them to assist in our future discovery and development efforts. These parties are not our employees and we cannot control the amount or timing of resources that they devote to our programs. If they fail to devote sufficient time and resources to our drug development programs or if their performance is substandard, it will delay the development and

commercialization of our product candidates. The parties with which we contract for execution of our clinical trials play a significant role in the conduct of the trials and the

subsequent collection and analysis of data. Their failure to meet their obligations could adversely affect clinical development of our product candidates. Moreover, these parties may also have relationships with other commercial entities, some of which may compete with us. If they assist our competitors, it could harm our competitive position.

If we lose our relationship with any one or more of these parties, we could experience a significant delay in both identifying another comparable provider and then contracting for its services. We may be unable to retain an alternative provider on reasonable terms, if at all. Even if we locate an alternative provider, it is likely that this provider may need additional time to respond to our needs and may not provide the same type or level of service as the original provider. In addition, any provider that we retain will be subject to current Good Laboratory Practices or cGLP, and similar foreign standards and we do not have control over compliance with these regulations by these providers. Consequently, if these practices and standards are not adhered to by these providers, the development and commercialization of our product candidates could be delayed.

We rely on a limited number of manufacturers for our product candidates and our business will be seriously harmed if these manufacturers are not able to satisfy our demand and alternative sources are not available.

We do not have an in-house manufacturing capability and depend completely on a small number of third-party manufacturers and active pharmaceutical ingredient formulators for the manufacture of our product candidates. We do not have long-term agreements with any of these third parties, and if they are unable or unwilling to perform for any reason, we may not be able to locate alternative acceptable manufacturers or formulators or enter into favorable agreements with them. Any inability to acquire sufficient quantities of our product candidates in a timely manner from these third parties could delay clinical trials and prevent us from developing our product candidates in a cost-effective manner or on a timely basis. In addition, manufacturers of our product candidates are subject to cGMP and similar foreign standards and we do not have control over compliance with these regulations by our manufacturers. If one of our contract manufacturers fails to maintain compliance, the production of our product candidates could be interrupted, resulting in delays and additional costs. In addition, if the facilities of such manufacturers do not pass a pre-approval plant inspection, the FDA will not grant approval of our products.

Our manufacturing strategy presents the following additional risks:

- because most of our third-party manufacturers and formulators are located outside of the United States, there may be difficulties in importing our compounds or their components into the United States as a result of, among other things, FDA import inspections, incomplete or inaccurate import documentation or defective packaging

- because of the complex nature of our compounds, our manufacturers may not be able to successfully manufacture our compounds in a cost-effective and/or timely manner

Materials necessary to manufacture our product candidates may not be available on commercially reasonable terms, or at all, which may delay the development, regulatory approval and commercialization of our product candidates.

We rely on our manufacturers to purchase from third-party suppliers the materials necessary to produce our product candidates for our clinical trials. Suppliers may not sell these materials to our manufacturers at the times we need them or on commercially reasonable terms. We do not have any control over the process or timing of the acquisition of these materials by our manufacturers. Moreover, we currently do not have any agreements for the commercial production of these materials. If our manufacturers are unable to obtain these materials for our clinical trials, product testing and potential regulatory approval of our product candidates could be delayed, significantly affecting our ability to develop our product candidates. If we or our manufacturers are unable to purchase these materials after regulatory

approval has been obtained for our product candidates, the commercial launch of our product candidates would be delayed or there would be a shortage in supply, which would materially affect our ability to generate revenues from the sale of our product candidates.

We face substantial competition which may result in others developing or commercializing products before or more successfully than we do.

Our future success will depend on our ability to demonstrate and maintain a competitive advantage with respect to our product candidates and our ability to identify and develop additional product candidates through the application of our pharmacogenetics and pharmacogenomics expertise. Large, fully integrated pharmaceutical companies, either alone or together with collaborative partners, have substantially greater financial resources and have significantly greater experience than we do in:

developing products

undertaking pre-clinical testing and clinical trials

obtaining FDA and other regulatory approvals of products

manufacturing and marketing products

These companies may invest heavily and quickly to discover and develop novel products that could make our product candidates obsolete. Accordingly, our competitors may succeed in obtaining patent protection, receiving FDA approval or commercializing superior products or other competing products before we do.

We believe the primary competitors for each of our product candidates are as follows:

For iloperidone in the treatment of schizophrenia, the atypical antipsychotics risperidone, including the depot formulation Risperdal® Consta®, and Invega® (paliperidone), each by Ortho-McNeil-Janssen Pharmaceuticals, Inc., Zyprexa® (olanzapine) by Eli Lilly and Company, Seroquel® (quetiapine) by AstraZeneca PLC, Abilify® (aripiprazole) by Bristol-Myers Squibb Company/Otsuka Pharmaceutical Co., Ltd., Geodon® (ziprasidone) by Pfizer Inc., and generic clozapine, as well as the typical antipsychotics haloperidol, chlorpromazine, thioridazine, and sulpiride (all of which are generic). In addition to the approved products, compounds in Phase III trials (or for which an NDA has been recently filed) for the treatment of schizophrenia include bifeprunox (Solvay S.A./Lundbeck A/S), and asenapine (Schering-Plough Corporation) and pimavanserin (Acadia Pharmaceuticals).

For tasimelteon in the treatment of insomnia, Rozerem™ (ramelteon) by Takeda Pharmaceuticals Company Limited, hypnotics such as Ambien® CR (zolpidem) by sanofi-aventis, Lunesta® (eszopiclone) by Sepracor Inc. and Sonata® (zaleplon) by King Pharmaceuticals, Inc., generic compounds such as zolpidem, trazodone and doxepin, and over-the-counter remedies such as Benadryl® and Tylenol PM®. In addition to the approved products, compounds in Phase III trials for insomnia (or for which an NDA has been recently filed) include indiplon (Neurocrine Biosciences, Inc.) low-dose doxepin (Silenor™) by Somaxon Pharmaceuticals, Inc. and Intermezza® (zolpidem tartarate sublingual lozenge) by Transcept Pharmaceuticals, Inc.

For tasimelteon in the treatment of depression, generic antidepressants such as paroxetine, sertraline, fluoxetine and buproprion, Lexapro® (escitalopram) by Lundbeck A/S /Forest Pharmaceuticals Inc., and Effexor® (venlafaxine) by Wyeth as well as other compounds such as Cymbalta® (duloxetine) by Eli Lilly and Valdoxan (agomelatine) by Novartis and Les Laboratories Servier.

Additionally, our ability to compete may be affected because insurers and other third-party payors in some cases seek to encourage the use of cheaper, generic products, which could make our products less attractive.

We have no experience selling, marketing or distributing products and no internal capability to do so.

At present, we have limited marketing and sales personnel. In order for us to commercialize any of our product candidates following regulatory approval, if any, we must either acquire or internally develop sales, marketing and distribution capabilities, or enter into collaborations with partners to perform these services for us. We may not be able to establish sales and distribution partnerships on acceptable terms or at all, and if we do enter into a distribution arrangement, our success will be dependent upon the performance of our partner. In the event that we attempt to acquire or develop our own in-house sales, marketing and distribution

capabilities, factors that may inhibit our efforts to commercialize our products without partners or licensees include:

- our inability to recruit and retain adequate numbers of effective sales and marketing personnel
- the inability of sales personnel to obtain access to or persuade adequate numbers of physicians to prescribe our product
- the lack of complementary products to be offered by our sales personnel, which may put us at a competitive disadvantage against companies with broader product lines
- unforeseen costs associated with creating our own sales and marketing team or with entering into a partnering agreement with an independent sales and marketing organization

We will need to increase the size of our organization upon regulatory approval of any of our product candidates, if any, and we may experience difficulties in managing this growth.

As of December 31, 2008, we had 24 full-time employees. While we have currently suspended our commercial activities and are operating under a reduced spending plan, if we resume our commercial activities, we will need to expand our managerial, operational, financial and other resources in order for us to manage and fund our operations, continue our development activities and commercialize our product candidates. Our current personnel, systems and facilities are not adequate to support this future growth. To manage our growth, we must:

- manage our clinical trials effectively
- manage our internal development efforts effectively
- improve our operational, financial, accounting and management controls, reporting systems and procedures
- build marketing and sales organizations in order to commercialize iloperidone
- attract and retain sufficient numbers of talented employees

We may be unable to successfully implement these tasks on a larger scale and, accordingly, may not achieve our development and commercialization goals.

If we cannot identify, or enter into licensing arrangements for, new product candidates, our ability to develop a diverse product portfolio may be limited.

A component of our business strategy is acquiring rights to develop and commercialize compounds discovered or developed by other pharmaceutical and biotechnology companies for which we may find effective uses and markets through our unique pharmacogenetics and pharmacogenomics expertise. Competition for the acquisition of these compounds is intense. If we are not able to identify opportunities to acquire rights to commercialize additional products, we may not be able to develop a diverse portfolio of products and our business may be harmed. Additionally, it may take substantial human and financial resources to secure commercial rights to promising product candidates. Moreover, if other firms develop pharmacogenetics and pharmacogenomics capabilities, we may face increased competition in identifying and acquiring additional product candidates.

If we lose key scientists or management personnel, or if we fail to recruit additional highly skilled personnel, it will impair our ability to identify, develop and commercialize product candidates.

We are highly dependent on principal members of our management team and scientific staff, including our Chief Executive Officer, Mihael H. Polymeropoulos, M.D. These executives each have significant pharmaceutical industry experience. The loss of any such executives, including Dr. Polymeropoulos, or any other principal member of our management team or scientific staff, would impair our ability to identify, develop and market new products.

Product liability lawsuits could divert our resources, result in substantial liabilities and reduce the commercial potential of our products.

The risk that we may be sued on product liability claims is inherent in the development of pharmaceutical products. For example, we face a risk of product liability exposure related to the testing of our product candidates in clinical trials and will face even greater risks upon any commercialization by us of our product candidates. We believe that we may be at a greater risk of product liability claims relative to other pharmaceutical companies because our compounds are intended to treat behavioral disorders, and it is possible that we may be held liable for the behavior and actions of patients who use our compounds. These lawsuits may divert our management from pursuing our business strategy and may be costly to defend. In addition, if we are held liable in any of these lawsuits, we may incur substantial liabilities and may be forced to limit or forego further commercialization of one or more of our products. Although we maintain product liability insurance, our aggregate coverage limit under this insurance is $5,000,000, and while we believe this amount of insurance is sufficient to cover our product liability exposure, these limits may not be high enough to fully cover potential liabilities. In addition, product liability insurance is becoming increasingly expensive, and we may not be able to obtain or maintain sufficient insurance coverage at an acceptable cost or otherwise to protect against potential product liability claims, which could prevent or inhibit the commercial production and sale of our products.

Legislative or regulatory reform of the healthcare system in the U.S. and foreign jurisdictions may affect our ability to sell our products profitably.

The continuing efforts of the U.S. and foreign governments, insurance companies, managed care organizations and other payors of health care services to contain or reduce health care costs may adversely affect our ability to set prices for our products which we believe are fair, and our ability to generate revenues and achieve and maintain profitability.

Specifically, in both the United States and some foreign jurisdictions there have been a number of legislative and regulatory proposals to change the healthcare system in ways that could affect our ability to sell our products profitably. In the United States, the Medicare Prescription Drug Improvement and Modernization Act of 2003 reforms the way Medicare will cover and reimburse for pharmaceutical products. This legislation could decrease the coverage and price that we may receive for our products. Other third-party payors are increasingly challenging the prices charged for medical products and services. It will be time-consuming and expensive for us to go through the process of seeking reimbursement from Medicare and private payors. Our products may not be considered cost effective, and coverage and reimbursement may not be available or sufficient to allow us to sell our products on a competitive and profitable basis. Further federal and state proposals and healthcare reforms are likely which could limit the prices that can be charged for the drugs we develop and may further limit our commercial opportunity. Our results of operations could be materially adversely affected by the Medicare prescription drug coverage legislation, by the possible effect of this legislation on amounts that private insurers will pay and by other healthcare reforms that may be enacted or adopted in the future.

In some foreign countries, including major markets in the European Union and Japan, the pricing of prescription pharmaceuticals is subject to governmental control. In these countries, pricing negotiations with governmental authorities can take nine to twelve months or longer after the receipt of regulatory marketing approval for a product. To obtain reimbursement or pricing approval in some countries, we may be required to conduct a clinical trial that compares the cost-effectiveness of our product candidate to other available therapies. Our business could be materially harmed if reimbursement of our products is unavailable or limited in scope or amount or if pricing is set at unsatisfactory levels.

Recently enacted legislation may make it more difficult and costly for us to obtain regulatory approval of our product candidates and to produce, to market and to distribute our existing products.

On September 27, 2007, then-President Bush signed into law the Food and Drug Administration Amendments Act of 2007 or the FDAAA. The FDAAA grants a variety of new powers to the FDA, many of

which are aimed at assuring drug safety and monitoring the safety of drug products after approval. The recently enacted amendments would among other things, require some new drug applicants to submit risk evaluation and minimization strategies to monitor and address potential safety issues for products upon approval, grant the FDA the authority to impose risk management measures for marketed products and to mandate labeling changes in certain circumstances, and establish new requirements for disclosing the results of clinical trials. Companies that violate the new law are subject to substantial civil monetary penalties. Additional measures have also been enacted to address the perceived shortcomings in the FDA s handling of drug safety issues, and to limit pharmaceutical company sales and promotional practices. While we expect the FDAAA to have a substantial effect on the pharmaceutical industry, the extent of that effect is not yet known. As the FDA issues regulations, guidance and interpretations relating to the new legislation, the impact on the industry as well as our business will become clearer. The new requirements and other changes that the FDAAA imposes may make it more difficult, and likely more costly, to obtain approval of new pharmaceutical products and to produce, market and distribute existing products. Our ability to commercialize approved products successfully may be hindered, and our business may be harmed as a result.

Our quarterly operating results may fluctuate significantly.

Our operating results will continue to be subject to quarterly fluctuations. The revenues we generate, if any, and our operating results will be affected by numerous factors, including:

- our addition or termination of development programs
- variations in the level of expenses related to our existing two product candidates or future development programs
- our execution of collaborative, licensing or other arrangements, and the timing of payments we may make or receive under these arrangements
- any intellectual property infringement lawsuit in which we may become involved
- regulatory developments affecting our product candidates or those of our competitors

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.

Risks related to intellectual property and other legal matters

Our rights to develop and commercialize our product candidates are subject in part to the terms and conditions of licenses or sublicenses granted to us by other pharmaceutical companies. With respect to tasimelteon, these terms and conditions include an option in favor of the licensor to reacquire rights to commercialize and develop these product candidates in certain circumstances.

Iloperidone is based in part on patents and other intellectual property owned by sanofi-aventis and Novartis. Titan Pharmaceuticals, Inc. (Titan) holds an exclusive license from sanofi-aventis to the intellectual property owned by sanofi-aventis, and Titan has sublicensed its rights under such license on an exclusive basis to Novartis. We have acquired exclusive rights to this and other intellectual property through a further sublicense from Novartis. Our rights with respect to the intellectual property to develop and commercialize iloperidone may terminate, in whole or in part, if we fail to meet certain milestones contained in our sublicense agreement with Novartis relating to the time it takes

for us to launch iloperidone commercially following regulatory approval, and the time it takes for us to receive regulatory approval following our submission of an NDA or equivalent foreign filing. We may also lose our rights to develop and commercialize iloperidone if we fail to pay royalties to Novartis, if we fail to comply with certain requirements in the sublicense agreement regarding our financial condition, or if we fail to comply with certain restrictions regarding our other development activities. Finally, our rights to develop and commercialize iloperidone may

be impaired if we do not cure breaches by Novartis and Titan of similar obligations contained in these sublicense and license agreements, although we are not aware of any such breach by Titan or Novartis. In the event of an early termination of our sublicense agreement, all rights licensed and developed by us under this agreement may be extinguished, which would have a material adverse effect on our business.

Tasimelteon is based in part on patents that we have licensed on an exclusive basis and other intellectual property licensed from Bristol-Myers Squibb Company (BMS). BMS holds certain rights with respect to tasimelteon in the license agreement. If we have not agreed to one or more partnering arrangements to develop and commercialize tasimelteon in certain significant markets with one or more third parties after the completion of the Phase III program, BMS has the option to exclusively develop and commercialize tasimelteon on its own on pre-determined financial terms, including milestone and royalty payments. BMS may terminate our license if we fail to meet certain milestones or if we otherwise breach our royalty or other obligations in the agreement. In the event that we terminate our license, or if BMS terminates our license due to our breach, all of our rights to tasimelteon (including any intellectual property we develop with respect to tasimelteon) will revert back to BMS or otherwise be licensed back to BMS on an exclusive basis. Any termination or reversion of our rights to develop or commercialize tasimelteon, including any reacquisition by BMS of our rights, may have a material adverse effect on our business

If our efforts to protect the proprietary nature of the intellectual property related to our products are not adequate, we may not be able to compete effectively in our markets.

In addition to the rights we have licensed from Novartis and BMS relating to our product candidates, we rely upon intellectual property we own relating to our products, including patents, patent applications and trade secrets. As of December 31, 2008 we had twenty-two pending provisional patent applications in the United States, five U.S. national stage applications under U.S.C. 371 and five pending Patent Cooperation Treaty applications, which permit the pursuit of patents outside of the U.S., relating to our product candidates in clinical development. Our patent applications may be challenged or fail to result in issued patents and our existing or future patents may be too narrow to prevent third parties from developing or designing around these patents. In addition, we rely on trade secret protection and confidentiality agreements to protect certain proprietary know-how that is not patentable, for processes for which patents are difficult to enforce and for any other elements of our drug development processes that involve proprietary know-how, information and technology that is not covered by patent applications. While we require all of our employees, consultants, advisors and any third parties who have access to our proprietary know-how, information and technology to enter into confidentiality agreements, we cannot be certain that this know-how, information and technology will not be disclosed or that competitors will not otherwise gain access to our trade secrets or independently develop substantially equivalent information and techniques. Further, the laws of some foreign countries do not protect proprietary rights to the same extent as the laws of the United States. As a result, we may encounter significant problems in protecting and defending our intellectual property both in the United States and abroad. If we are unable to protect or defend the intellectual property related to our technologies, we will not be able to establish or maintain a competitive advantage in our market.

If we do not obtain protection under the Hatch-Waxman Act and similar foreign legislation to extend our patents and to obtain market exclusivity for our product candidates, our business will be materially harmed.

The United States Drug Price Competition and Patent Term Restoration Act of 1984, more commonly known as the Hatch-Waxman Act, provides for an extension of patent protection for drug compounds for a period of up to five years to compensate for time spent in development. Assuming we gain a five-year extension for each of our current product candidates in clinical development, and that we continue to have rights under our sublicense and license agreements with respect to these product candidates, we would have exclusive rights to iloperidone s United States new chemical entity patent (the primary patent covering the compound as a new composition of matter) until 2016 and to tasimelteon s United States new chemical entity patent until 2022. In Europe, similar legislative enactments allow

patent protection in the European Union to be extended for up to five years through the grant of a Supplementary Protection Certificate. Assuming we gain such a five-year extension for each of our current product candidates in clinical development, and that we continue to have rights

under our sublicense and license agreements with respect to these product candidates, we would have exclusive rights to iloperidone s European new chemical entity patents until 2015 and to tasimelteon s European new chemical entity patents until 2022. Additionally, a directive in the European Union provides that companies who receive regulatory approval for a new compound will have a 10-year period of market exclusivity for that compound (with the possibility of a further one-year extension) in most countries in Europe, beginning on the date of such European regulatory approval, regardless of when the European new chemical entity patent covering such compound expires. A generic version of the approved drug may not be marketed or sold in Europe during such market exclusivity period. This directive may be of particular importance with respect to iloperidone, since the European new chemical entity patent for iloperidone will likely expire prior to the end of this 10-year period of market exclusivity. However, there is no assurance that we will receive the extensions of our patents or other exclusive rights available under the Hatch-Waxman Act or similar foreign legislation. If we fail to receive such extensions and exclusive rights, our ability to prevent competitors from manufacturing, marketing and selling generic versions of our products will be materially harmed.

Litigation or third-party claims of intellectual property infringement could require us to divert resources and may prevent or delay our drug discovery and development efforts.

Our commercial success depends in part on our not infringing the patents and proprietary rights of third parties. Third parties may assert that we are employing their proprietary technology without authorization. In addition, third parties may obtain patents in the future and claim that use of our technologies infringes upon these patents. Furthermore, parties making claims against us may obtain injunctive or other equitable relief, which could effectively block our ability to develop and commercialize one or more of our product candidates. Defense of these claims, regardless of their merit, would divert substantial financial and employee resources from our business. In the event of a successful claim of infringement against us, we may have to pay substantial damages, obtain one or more licenses from third parties or pay royalties. In addition, even in the absence of litigation, we may need to obtain additional licenses from third parties to advance our research or allow commercialization of our product candidates. We may fail to obtain any of these licenses at a reasonable cost or on reasonable terms, if at all. In that event, we would be unable to develop and commercialize further one or more of our product candidates.

In addition, in the future we could be required to initiate litigation to enforce our proprietary rights against infringement by third parties. Prosecution of these claims to enforce our rights against others could divert substantial financial and employee resources from our business. If we fail to enforce our proprietary rights against others, our business will be harmed.

If we use hazardous and biological materials in a manner that causes injury or violates applicable law, we may be liable for damages.

Our research and development activities involve the controlled use of potentially hazardous substances, including toxic chemical and biological materials. We could be held liable for any contamination, injury or other damages resulting from these hazardous substances. In addition, our operations produce hazardous waste products. While third parties are responsible for disposal of our hazardous waste, we could be liable under environmental laws for any required cleanup of sites at which our waste is disposed. Federal, state, foreign and local laws and regulations govern the use, manufacture, storage, handling and disposal of these hazardous materials. If we fail to comply with these laws and regulations at any time, or if they change, we may be subject to criminal sanctions and substantial civil liabilities, which may adversely affect our business.

Even if we continue to comply with all applicable laws and regulations regarding hazardous materials, we cannot eliminate the risk of accidental contamination or discharge and our resultant liability for any injuries or other damages caused by these accidents. Although we maintain pollution liability insurance, our coverage limit under this insurance

is $2,000,000, and while we believe this amount and type of insurance is sufficient to cover risks typically associated with our handling of materials, the insurance may not cover all environmental liabilities, and these limits may not be high enough to cover potential liabilities for these damages fully. The amount of uninsured liabilities may exceed our financial resources and materially harm our business.

Risks related to our common stock

Our stock price has been volatile and may be volatile in the future, and purchasers of our common stock could incur substantial losses.

The stock market has from time to time experienced significant price and volume fluctuations, and the market prices of the securities of life sciences companies without product revenues, such as ours, have historically been highly volatile. Between December 31, 2007 and December 31, 2008, the high and low sale prices of our common stock as reported on the NASDAQ Global Market varied between $7.13 and $0.45. The following factors, in addition to the other risk factors described in this section, may also have a significant impact on the market price of our common stock:

- publicity regarding actual or potential testing or trial results relating to products under development by us or our competitors
- the outcome of regulatory review relating to products under development by us or our competitors
- regulatory developments in the United States and foreign countries
- developments concerning any collaboration or other strategic transaction we may undertake
- announcements of patent issuances or denials, technological innovations or new commercial products by us or our competitors
- actual or anticipated variations in our quarterly operating results
- changes in estimates of our financial results or recommendations by securities analysts
- additions or departures of key personnel or members of our board of directors
- publicity regarding actual or potential transactions involving the Company
- economic and other external factors beyond our control

As a result of these factors, holders of our common stock might be unable to sell their shares at or above the price they paid for such shares.

If there are substantial sales of our common stock, our stock price could decline.

A small number of institutional investors and private equity funds hold a significant number of shares of our common stock. Sales by these stockholders of a substantial number of shares, or the expectation of such sales, could cause a significant reduction in the market price of our common stock. Additionally, a small number of early investors in our company 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.

In addition to our outstanding common stock, as of December 31, 2008, there were a total of 4,453,629 shares of common stock that we have registered and that we are obligated to issue upon the exercise of currently outstanding options granted under our Second Amended and Restated Management Equity Plan and 2006 Equity Incentive Plan.

Upon the exercise of these options in accordance with their respective terms, these shares may be resold freely, subject to restrictions imposed on our affiliates under Rule 144. If significant sales of these shares occur in short periods of time, these sales could reduce the market price of our common stock. Any reduction in the trading price of our common stock could impede our ability to raise capital on attractive terms.

If we fail to maintain the requirements for continued listing on the NASDAQ Global Market, our common stock could be delisted from trading, which would adversely affect the liquidity of our common stock and our ability to raise additional capital.

Our common stock is currently listed for quotation on the NASDAQ Global Market. We are required to meet specified financial requirements in order to maintain our listing on the NASDAQ Global Market. One such requirement is that we maintain a minimum closing bid price of at least $1.00 per share for our common

stock. Our common stock has recently closed at prices below the minimum bid requirement. If the closing bid price of a share of the Company s common stock were to fall below $1.00 for a period of thirty (30) consecutive business days, the Company would receive a deficiency notice from NASDAQ advising us that we have 180 calendar days to regain compliance by maintaining a minimum closing bid price of at least $1.00 for a minimum of ten consecutive business days. Under certain circumstances, NASDAQ could require that the minimum closing bid price exceed $1.00 for more than ten consecutive days before determining that a company complies with its continued listing standards. On October 16, 2008, NASDAQ announced that, effective as of such date and through Friday, January 16, 2009, it has suspended the enforcement of the rules requiring a minimum $1.00 closing bid price. NASDAQ has extended its suspension of the rules requiring a minimum $1.00 closing bid price. These rules will be reinstated on Monday, April 20, 2009. If in the future, we fail to satisfy the NASDAQ Global Market s continued listing requirements, our common stock could be delisted from the NASDAQ Global Market, in which case we may transfer to the NASDAQ Capital Market, which generally has lower financial requirements for initial listing or, if we fail to meet its listing requirements, the over-the-counter bulletin board. There are many factors that may adversely affect our minimum bid price, including those described in Item 1A Risk Factors of Part I of this annual report on Form 10-K/A, which contains a more complete discussion of those factors and other risks. Many of these factors are outside of our control. As a result, we may not be able to sustain compliance with the minimum bid price rule in the long term. Any potential delisting of our common stock from the NASDAQ Global Market would make it more difficult for our stockholders to sell our stock in the public market and would likely result in decreased liquidity and increased volatility for our common stock.

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

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

Anti-takeover provisions in our charter and bylaws, and in Delaware law, and our rights plan could prevent or delay a change in control of our company.

We are a Delaware corporation and the anti-takeover provisions of Section 203 of the Delaware General Corporation Law may discourage, delay or prevent a change in control by prohibiting us from engaging in a business combination with an interested stockholder for a period of three years after the person becomes an interested stockholder, even if a change of control would be beneficial to our existing stockholders. In addition, our amended and restated certificate of incorporation and bylaws may discourage, delay or prevent a change in our management or control over us that stockholders may consider favorable. Our amended and restated certificate of incorporation and bylaws:

- authorize the issuance of blank check preferred stock that could be issued by our board of directors to thwart a takeover attempt
- do not provide for cumulative voting in the election of directors, which would allow holders of less than a majority of the stock to elect some directors
- establish a classified board of directors, as a result of which the successors to the directors whose terms have expired will be elected to serve from the time of election and qualification until the third annual meeting following their election

require that directors only be removed from office for cause

provide that vacancies on the board of directors, including newly-created directorships, may be filled only by a majority vote of directors then in office

limit who may call special meetings of stockholders

prohibit stockholder action by written consent, requiring all actions to be taken at a meeting of the stockholders

establish advance notice requirements for nominating candidates for election to the board of directors or for proposing matters that can be acted upon by stockholders at stockholder meetings

Moreover, on September 25, 2008, our board of directors adopted a rights agreement, the provisions of which could result in significant dilution of the proportionate ownership of a potential acquirer and, accordingly, could discourage, delay or prevent a change in our management or control over us.

We may lose some or all of the value of some of our marketable securities.

We engage one or more third parties to manage some of our cash consistent with an investment policy that allows a range of investments and maturities. The investments are intended to preserve principal while providing liquidity adequate to meet projected cash requirements. Risks of principal loss are intended to be minimized through diversified short and medium term investments of high quality, but the investments are not, in every case, guaranteed or fully insured. In light of recent changes in the credit market, some high quality short-term investment securities, similar to the types of securities that we invest in, have suffered illiquidity or events of default. From time to time, we may suffer losses on our marketable securities, which could have a material adverse impact on our operations.

Unstable market conditions may have serious adverse consequences on our business.

The recent economic downturn and market instability has made the business climate more volatile and more costly. Our general business strategy may be adversely affected by unpredictable and unstable market conditions. If the current equity and credit markets deteriorate further, or do not improve, it may make any necessary debt or equity financing more difficult, more costly, and more dilutive. While we believe we have adequate capital resources to meet current working capital and capital expenditure requirements, a lingering economic downturn or significant increase in our expenses could require additional financing on less than attractive rates or on terms that are excessively dilutive to existing stockholders. Failure to secure any necessary financing in a timely manner and on favorable terms could have a material adverse effect on our stock price and could require us to delay or abandon clinical development plans.

There is a risk that one or more of our current service providers, manufacturers and other partners may encounter difficulties during challenging economic times, which would directly affect our ability to attain our operating goals on schedule and on budget.

One of our stockholders has notified us that it intends to nominate a competing slate of directors for election at this year s annual meeting of stockholders and to propose resolutions to our stockholders relating to our bylaws and the ongoing operations of our company.

On February 13, 2009, we received two letters from one of our stockholders, Tang Capital Partners, LP (TCP), stating its intent to, among other things, nominate two directors to stand for election at our 2009 annual meeting of stockholders and submit proposals at the annual meeting to amend our bylaws and request that our board of directors take action to liquidate the Company. TCP seeks to replace two directors, our current Chief Executive Officer and the Chairman of our board.

TCP has also notified us that it intends to propose a series of amendments to our bylaws which, if approved by the affirmative vote of at least 80% of the voting power of all of the outstanding shares of capital stock of the Company entitled to vote generally in the election of directors, would require unanimous approval of the members of the board of directors for a number of critical operating matters, including raising capital, executing material contracts, and

hiring certain key employees. If the proposed bylaw amendments are approved, it will be very difficult for us to implement our current strategy and further the development of our compounds because, not withstanding a consensus on the board, any one director, whether nominated by the board, TCP or any other stockholder, will have a veto on these and other critical operating matters.

In addition, TCP has requested that our board of directors take action to liquidate the Company and distribute the remaining cash to our stockholders. If we fail to take such action, TCP or other stockholders may attempt to compel a liquidation of the Company through litigation or some other means. Such litigation could result in substantial costs and divert management s attention and resources, which could harm our business, operating results and financial conditions.

ITEM 1B. UNRESOLVED STAFF COMMENTS

Not applicable.

ITEM 2. PROPERTIES

Our current headquarters are located in Rockville, Maryland, consisting of approximately 27,000 square feet of office and laboratory space. Our lease for this facility expires in 2016.

Management believes that the leased facilities are suitable and adequate to meet the Company s anticipated needs.

ITEM 3. LEGAL PROCEEDINGS

The Company is not a party to any material pending legal proceedings, and management is not aware of any contemplated proceedings by any governmental authority against the Company.

ITEM 4. SUBMISSION OF MATTERS TO A VOTE OF SECURITY HOLDERS

None.

PART II

ITEM 5. MARKET FOR REGISTRANT S COMMON EQUITY, RELATED SHAREHOLDER MATTERS AND ISSUER PURCHASES OF EQUITY SECURITIES

Our common stock is quoted on The NASDAQ Global Market under the symbol VNDA. The following table sets forth, for the periods indicated, the range of high and low sale prices of our common stock as reported on The NASDAQ Global Market.

Year Ended December 31, 2007	**High**	**Low**
First quarter 2007	$ 32.00	$ 21.69
Second quarter 2007	$ 24.31	$ 18.75
Third quarter 2007	$ 21.50	$ 13.23
Fourth quarter 2007	$ 19.40	$ 6.49

Year Ended December 31, 2008	**High**	**Low**
First quarter 2008	$ 7.13	$ 2.70
Second quarter 2008	$ 6.59	$ 2.98
Third quarter 2008	$ 4.03	$ 0.76

Fourth quarter 2008	$ 1.02	$ 0.45

As of March 11, 2009, there were 27 holders of record of our common stock.

Dividends

The Company has not paid dividends to its shareholders (other than a dividend of preferred share purchase rights which was declared on September 25, 2008) since its inception and does not plan to pay dividends in the foreseeable future. The Company currently intends to retain earnings, if any, to finance the growth of the Company.

Market Price of and Dividends on the Registrant s Common Equity and Related Stockholder Matters

The following graph shows the cumulative total return, assuming the investment of $100 on April 12, 2006 (the date of the initial public offering) on an investment in each of the Company s common stock, the NASDAQ Composite Index and the Amex Biotechnology Index (in either case, assuming reinvestment of dividends). The comparisons in the table are required by the SEC and are not intended to forecast or be indicative of possible future performance of the Company s common stock. We have not paid dividends to our stockholders since the inception and do not plan to pay dividends in the foreseeable future. The following graph and related information is being furnished solely to accompany this Form 10-K/A pursuant to Item 201(e) of Regulation S-K and shall not be deemed soliciting materials or to be filed with the SEC (other than as provided in Item 201), nor shall such information be incorporated by reference into any of our filings under the Securities Act of 1933 or the Securities Exchange Act of 1934, whether made before or after the date hereof, and irrespective of any general incorporation language in any such filing.

ITEM 6. SELECTED CONSOLIDATED FINANCIAL DATA

The consolidated statements of operations data for the years ended December 31, 2008, 2007 and 2006 and the consolidated balance sheet data as of December 31, 2008 and 2007 are each derived from our audited consolidated financial statements included in this annual report on Form 10-K/A. The consolidated statements of operations data for the years ended December 31, 2005, 2004 and for the period from March 13, 2003 (inception) to December 31, 2003 and the consolidated balance sheet data as of December 31, 2006, 2005, 2004 and 2003 are each derived from our audited consolidated financial statements not included herein. Our historical results for any prior period are not necessarily indicative of results to be expected in any future period.

The following data should be read together with our consolidated financial statements and accompanying notes and the section entitled Management s discussion and analysis of financial condition and results of operations included in this annual report on Form 10-K/A.

	Year Ended December 31,					Period from March 13, 2003 (Inception) to December 31, 2003
	2008	2007	2006	2005	2004	
Statements of operations data						
Revenue	$	$	$	$	$ 33,980	$ 47,565
Operating expenses:						
Research and development	23,935,541	47,234,867	52,070,776	16,890,615	7,442,983	2,010,532
General and administrative	28,909,580	32,803,508	13,637,664	7,396,038	2,119,394	1,052,659
Total operating expenses	52,845,121	80,038,375	65,708,440	24,286,653	9,562,377	3,063,191
Loss from operations	(52,845,121)	(80,038,375)	(65,708,440)	(24,286,653)	(9,528,397)	(3,015,626)
Total other income, net	1,780,880	5,978,564	2,197,821	410,001	59,060	44,805
Loss before tax provision	(51,064,241)	(74,059,811)	(63,510,619)	(23,876,652)	(9,469,337)	(2,970,821)
Tax provision		9,879	549	7,649	4,949	
Net loss	(51,064,241)	(74,069,690)	(63,511,168)	(23,884,301)	(9,474,286)	(2,970,821)
Beneficial conversion feature-deemed dividend to preferred stockholders(1)				(33,486,623)		
Net loss attributable to common stockholders	$ (51,064,241)	$ (74,069,690)	$ (63,511,168)	$ (57,370,924)	$ (9,474,286)	$ (2,970,821)
Basic and diluted net loss per share applicable to common stockholders	$ (1.92)	$ (2.81)	$ (3.97)	$ (3,374.33)	$ (3,137.18)	$ (983.72)

Shares used in calculation of basic and diluted net loss per shares attributable to common stockholders	26,650,126	26,360,177	16,001,815	17,002	3,020	3,020

(1) In September and December of 2005, we completed the sale of an additional 27,235,783 shares of Series B preferred stock for net proceeds of approximately $33.5 million. After evaluating the fair value of the common stock obtainable upon conversion by the stockholders, we determined that the issuance of the Series B preferred stock sold in 2005 resulted in a beneficial conversion feature which was fully accreted in 2005 and is recorded as a deemed dividend to preferred stockholders of approximately $33.5 million for the year ended December 31, 2005.

	As of December 31,					
	2008	**2007**	**2006**	**2005**	**2004**	**2003**
Balance sheet data						
Cash and cash equivalents	$ 39,079,304	$ 41,929,533	$ 30,928,895	$ 21,012,815	$ 16,259,770	$ 7,165,722
Marketable securities	7,378,798	51,223,291	941,981	10,141,189		
Working capital	44,334,703	74,177,567	24,714,285	28,308,434	14,827,621	6,204,248
Total assets	49,933,843	96,860,780	36,260,276	35,752,770	17,752,241	8,385,913
Total liabilities	3,913,569	13,131,849	9,503,404	5,087,963	1,808,654	1,378,880
Convertible preferred stock				61,795,187	28,308,564	9,963,541
Deficit accumulated during the development stage	(224,974,507)	(173,910,266)	(99,840,576)	(36,329,408)	(12,445,107)	(2,970,821)
Total stockholders equity	46,020,274	83,728,931	26,756,872	30,664,807	15,943,587	7,007,033

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

You should read the following discussion and analysis of our financial condition and results of operations together with Selected Consolidated Financial Data and our consolidated financial statements and related notes appearing at the end of this annual report on Form 10-K/A. Some of the information contained in this discussion and analysis or set forth elsewhere in this annual report on Form 10-K/A include historical information and other information with respect to our plans and strategy for our business and contain forward-looking statements that involve risk, 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 the Risk Factors section of this report and elsewhere in this annual report on Form 10-K/A.

Overview

We are a biopharmaceutical company focused on the development and commercialization of clinical-stage product candidates for central nervous system disorders, with exclusive worldwide commercial rights to two product candidates in clinical development. Our lead product candidate, iloperidone, is a compound for the treatment of schizophrenia. On November 27, 2007, the United States Food and Drug Administration (FDA) accepted our New Drug Application (NDA) for iloperidone in schizophrenia. In July 2008, we announced that the FDA had determined that our NDA was not approvable and indicated, among other things, that we would have to conduct additional studies and submit that data before the FDA would approve iloperidone for commercial sale for the treatment of schizophrenia. In September 2008, we met with the FDA to discuss the FDA s determination. The FDA asked us to provide a complete response to the not-approvable letter, which we submitted on November 6, 2008. The FDA accepted the complete response for review and has set a new target action date of May 6, 2009. There are no guarantees that the FDA will provide its response by May 6, 2009, nor can there be any assurances that any such response will be favorable. Pending the FDA s reply to our complete response, we have suspended all non-essential iloperidone-related activities. Our second product candidate, tasimelteon is a compound for the treatment of sleep and mood disorders. In November 2006, we announced positive top-line results from our Phase III trial of tasimelteon in transient insomnia. In June 2008, the Company announced positive top-line results from the Phase III trial of tasimelteon in chronic primary insomnia. Tasimelteon is also ready for Phase II trials for the treatment of depression.

We will have to conduct additional Phase III trials for tasimelteon in chronic sleep disorders prior to our filing of an NDA for tasimelteon. Assuming successful outcomes of our clinical trials and approval by the FDA, we expect to commercialize iloperidone with our own sales force and/or commercial partners in the United States, and to seek partners for commercialization of the compound outside of the United States. Given the range of potential indications for tasimelteon, we intend to pursue one or more partnerships for the development and commercialization of tasimelteon worldwide.

We are a development stage enterprise and have accumulated net losses of approximately $225.0 million since the inception of our operations through December 31, 2008. We have no product revenues to date and have no approved products for sale. Since we began our operations in March 2003, we have devoted substantially all of our resources to the in-licensing and clinical development of our product candidates. Our future operating results will depend largely on our ability to successfully develop and commercialize our lead product candidate, iloperidone, and on the progress of other product candidates currently in our research and development pipeline. The results of our operations will vary significantly from year-to-year and quarter-to-quarter and depend on a number of factors, including risks related to our business, risks related to our industry, and other risks which are detailed in Item 1A of Part I of this report, entitled Risk Factors.

We completed our initial public offering in April 2006. The offering totaled 5,964,188 shares of common stock at a public offering price of $10.00, resulting in net proceeds to the Company of approximately $53.3 million, after deducting underwriters discounts and commissions as well as offering expenses. Upon completion of the initial public offering, all shares of the Company s Series A preferred stock and Series B preferred stock were converted into an aggregate of 15,794,632 shares of common stock.

In January 2007 we completed our follow-on offering, consisting of 4,370,000 shares of common stock at a public offering price of $27.29 per share, resulting in net proceeds to the Company of approximately $111.3 million after deducting underwriting discounts and commissions and offering expenses.

Our activities will necessitate significant uses of working capital for the foreseeable future. Our capital requirements will depend on many factors, including the success of our research and development efforts, the satisfaction of certain regulatory requirements, payments received under contractual agreements with other parties, if any, and the status of competitive products. However, given the receipt of the not-approvable letter from the FDA with respect to the NDA for iloperidone, and that any additional studies required by the FDA prior to its approval of iloperidone would require significant capital in excess of our currently available resources, we are now operating under a reduced spending plan. On December 16, 2008, we committed to a plan of termination that resulted in a work force reduction of 17 employees, including two officers, in order to reduce operating costs. As of December 31, 2008, the Company employed 24 full-time employees. This represents approximately a 55% decrease from the 53 employees the Company had on August 1, 2008. We believe that, if we continue to operate under our reduced spending plan, our existing cash, cash equivalents and marketable securities will be sufficient to fund operations at least through the second quarter 2010. In budgeting for our activities, we have relied on a number of assumptions, including assumptions that we will not conduct any additional clinical trials for either of the oral or injectable formulations of iloperidone, that we will not engage in any further commercial activities related to iloperidone, that we will not engage in further in-licensing activities, that we will not receive any proceeds from potential partnerships, that we will not conduct additional trials for tasimelteon, that we will be able to retain our key personnel, that we will continue to seek FDA approval of iloperidone, that we will continue to evaluate clinical and pre-clinical compounds for potential development, and that we will not incur any significant contingent liabilities.

We may need to raise additional funds if one or more of our assumptions proves to be incorrect or if we choose to resume our commercialization efforts with respect to iloperidone, expand our product development efforts, conduct additional clinical trials for one or more of our product candidates or seek to acquire additional product candidates, and we may decide to raise additional funds even before they are needed if the conditions for raising capital are favorable. In our capital-raising efforts, we may seek to sell additional equity or debt securities or obtain a bank credit facility. The sale of additional equity or debt securities, if convertible, could result in dilution to our stockholders. The incurrence of indebtedness would result in increased fixed obligations and could also result in covenants that would restrict our operations. However, we may not be able to raise additional funds on acceptable terms, or at all. Given the current global economic climate, we may have more difficulty raising funds than we would during a period of economic stability. If we are unable to secure sufficient capital to fund our research and development activities, we may not be able to continue operations, or we may have to enter into collaboration agreements that could require us to share commercial rights to our products to a greater extent or at earlier stages in the drug development process than is currently intended. These collaborations, if consummated prior to proof-of-efficacy or safety of a given product candidate, could impair our ability to realize value from that product candidate.

Iloperidone. Iloperidone is our product candidate under development to treat schizophrenia. We submitted an NDA for iloperidone for the treatment of schizophrenia to the FDA on September 27, 2007 and on November 27, 2007, the FDA accepted our NDA. The application included data from 35 clinical trials and more than 3,000 patients treated with iloperidone and also contained pharmacogenetic data aimed to further improve the benefit/risk profile of iloperidone in the treatment of patients with schizophrenia. In July 2008, we announced that the FDA had determined that our NDA was not approvable and indicated, among other things, that we would have to conduct additional studies and submit that data before the FDA would approve iloperidone for commercial sale for the treatment of schizophrenia. Performance and completion of these additional studies will require years of testing and, even if positive results are achieved, may not result in the FDA s approval of iloperidone. In September 2008, we met with the FDA to discuss the FDA s determination. The FDA asked us to provide a complete response to the not-approvable letter, which we submitted on November 6, 2008. The FDA accepted the complete response for review and has set a

new target action date of May 6, 2009. There are no guarantees that the FDA will provide its response by May 6, 2009, nor can there

be any assurances that any such response will be favorable. Pending the FDA s reply to our complete response, we have suspended all non-essential iloperidone-related activities.

From inception to December 31, 2008 we incurred approximately $74.5 million in research and development costs directly attributable to our development of iloperidone, including a $5.0 million milestone license fee paid to Novartis in 2007 upon the acceptance of our NDA.

We are also developing a 4-week injectable formulation for iloperidone, for which we already have early Phase II data from a study previously conducted by Novartis. We have completed essential manufacturing activities and intend to conduct additional clinical trials if and when, we receive following FDA approval of the oral dose formulation for iloperidone. If the FDA approves the oral formulation of iloperidone, we intend to resume the development of the injectable formulation and we believe we will need to conduct additional trials with this formulation to be able to file for FDA approval.

Tasimelteon. Tasimelteon is our product candidate under development to treat sleep and mood disorders. Tasimelteon is a melatonin receptor agonist that works by adjusting the human body clock of circadian rhythm. Tasimelteon has successfully completed a Phase III trial for the treatment of transient insomnia in November 2006. In June 2008, we announced positive top-line results from the Phase III trial of tasimelteon in chronic primary insomnia. The trial was a randomized, double-blind, and placebo-controlled study with 324 patients. The trial measured time to fall asleep and sleep maintenance, as well as next-day performance. We will have to conduct additional trials prior to our filing of an NDA for tasimelteon to treat sleep disorders. Tasimelteon is also ready for Phase II trials for the treatment of depression.

From inception to December 31, 2008, we incurred approximately $51.3 million in direct research and development costs directly attributable to our development of tasimelteon, including a $1.0 million milestone license fee paid to BMS in 2006 upon the initiation of our Phase III program.

VSF-173. On November 3, 2008, we received written notice from Novartis that our license agreement with respect to VSF-173 had terminated in accordance with its terms as a result of our failure to satisfy a specific development milestone within the time period specified in the license agreement. As a result, we no longer have any rights with respect to VSF-173 and Novartis has a non-exclusive worldwide license to all information and intellectual property generated by us or on our behalf related to our development of VSF-173. We are currently evaluating any options that we may have with respect to VSF-173, which may include the possibility of entering into a new license agreement or other arrangement with Novartis to allow us to resume our development of VSF-173; however, there can be no assurance that we will be able to enter into such an agreement or arrangement on acceptable terms, or at all.

From inception to December 31, 2008, we incurred approximately $6.7 million in research and development costs directly attributable to our development of VSF-173, including a milestone license fee of $1.0 million paid to Novartis upon the initiation of our first Phase II clinical trial in March of 2007.

Revenues. We generated some revenue during the period from March 13, 2003 (inception) to December 31, 2003 and during the year ended December 31, 2004 under research and development contracts that were derived principally from consulting agreements we entered into during our start-up phase to defray research costs. We completed our obligations during those periods under these agreements and no longer seek such arrangements.

We have not generated any other operating revenue since our inception. Any revenue that we may receive in the near future is expected to consist primarily of license fees, milestone payments and research and development reimbursement payments to be received from potential partners. If our development efforts result in clinical success, regulatory approval and successful commercialization of our products, we could generate revenue from sales of our

products and from receipt of royalties on sales of licensed products.

Research and development expenses. Our research and development expenses consist primarily of fees paid to third-party professional service providers in connection with the services they provide for our clinical trials, costs of contract manufacturing services, costs of materials used in clinical trials and research and development, costs for regulatory consultants and filings, depreciation of capital resources used to develop our

products, all related facilities costs, and salaries, benefits and stock-based compensation expenses related to our research and development personnel. We expense research and development costs as incurred, including payments made to date under our license agreements. We believe that significant investment in product development is a competitive necessity and plan to continue these investments in order to realize the potential of our product candidates and pharmacogenetics and pharmacogenomics expertise. From inception through December 31, 2008, we incurred research and development expenses in the aggregate of approximately $150.0 million, including stock-based compensation expenses of approximately $7.5 million. We expect our research and development expenses to increase as we continue to develop our product candidates. We also expect to incur licensing costs in the future that could be substantial, as we continue our efforts to develop our product candidates and to evaluate potential in-license product candidates.

The following table summarizes our product development initiatives for the years ended December 31, 2008 to December 31, 2004 and the period from March 13, 2003 (inception) to December 31, 2003 and for the period from March 13, 2003 (inception) to December 31, 2008. Included in the following table are the research and development expenses recognized in connection with our product candidates in clinical development. Included in Other product candidates are the costs directly related to research initiatives for all other product candidates.

	Year Ended December 31, 2008	Year Ended December 31, 2007	Year Ended December 31, 2006	Year Ended December 31, 2005	Year Ended December 31, 2004	March 13, 2003 (Inception) to December 31, 2003(2)	Period from March 13, 2003 (Inception) to December 31, 2008
Direct project costs(1)							
iloperidone	$ 8,485,000	$ 20,668,000	$ 36,455,000	$ 7,798,000	$ 1,123,000	$	$ 74,529,000
tasimelteon	11,344,000	18,947,000	11,665,000	6,133,000	3,221,000		51,310,000
VSF-173	737,000	3,404,000	1,058,000	943,000	568,000		6,710,000
Other product candidates	1,443,000	2,095,000	1,098,000	899,000	1,037,000		6,572,000
Total direct product costs	22,009,000	45,114,000	50,276,000	15,773,000	5,949,000		139,121,000
Indirect project costs(1)							
Facility(3)	683,000	495,000	578,000	247,000	259,000		2,262,000
Depreciation	330,000	423,000	474,000	375,000	345,000	69,000	2,016,000
Other indirect overhead costs	913,000	1,203,000	743,000	496,000	890,000	1,941,000	6,186,000

Total indirect expenses	1,926,000	2,121,000	1,795,000	1,118,000	1,494,000	2,010,000	10,464,000
Total research and development expenses	$ 23,935,000	$ 47,235,000	$ 52,071,000	$ 16,891,000	$ 7,443,000	$ 2,010,000	$ 149,585,000

(1) Many of our research and development costs are not attributable to any individual project because we share resources across several development projects. We record direct costs, including personnel costs and related benefits and stock-based compensation, on a project-by-project basis. We record indirect costs that support a number of our research and development activities in the aggregate.

(2) In 2003, there were no active development programs in process for our product candidates listed in the table.

(3) In 2003, all facility-related costs were allocated to general and administrative expenses.

General and administrative expenses. General and administrative expenses consist primarily of salaries and other related costs for personnel, including stock-based compensation, serving executive, finance, accounting, information technology, marketing and human resource functions. Other costs include facility costs not otherwise included in research and development expenses and fees for legal, accounting and other professional services. We expect our general and administrative expenses to decrease in 2009 as we operate under a reduced spending plan pending a response from the FDA to our complete response to the not-

approvable letter related to iloperidone. From inception through December 31, 2008, we incurred general and administrative expenses in the aggregate of approximately $85.9 million, including stock-based compensation expenses of approximately $36.6 million.

Interest and other income, net. Interest income consists of interest earned on our cash and cash equivalents, marketable securities and restricted cash. Interest expense consists of interest incurred on equipment debt.

Critical accounting policies

The preparation of our consolidated financial statements requires us to make estimates and assumptions that affect the reported amounts of assets and liabilities and the disclosure of contingent assets and liabilities at the date of our financial statements, as well as the reported revenues and expenses during the reported periods. We base our estimates on historical experience and on various other factors that we believe are reasonable under the circumstances, the results of which form the basis for making judgments about the carrying value of assets and liabilities that are not apparent from other sources. Actual results may differ from these estimates under different assumptions or conditions.

Our significant accounting policies are described in the notes to our audited consolidated financial statements for the year ended December 31, 2008 included in this annual report on Form 10-K/A. However, we believe that the following accounting policies are important to understanding and evaluating our reported financial results, and we have accordingly included them in this discussion.

Accrued expenses. As part of the process of preparing financial statements we are required to estimate accrued expenses. The estimation of accrued expenses involves identifying services that have been performed on our behalf, and then estimating the level of service performed and the associated cost incurred for such services as of each balance sheet date in the financial statements. Accrued expenses include professional service fees, such as lawyers and accountants, contract service fees, such as those under contracts with clinical monitors, data management organizations and investigators in conjunction with clinical trials, fees to contract manufacturers in conjunction with the production of clinical materials, and fees for marketing and other commercialization activities. Pursuant to our assessment of the services that have been performed on clinical trials and other contracts, we recognize these expenses as the services are provided. Our assessments include, but are not limited to: (1) an evaluation by the project manager of the work that has been completed during the period, (2) measurement of progress prepared internally and/or provided by the third-party service provider, (3) analyses of data that justify the progress, and (4) management s judgment. In the event that we do not identify certain costs that have begun to be incurred or we under- or over-estimate the level of services performed or the costs of such services, our reported expenses for such period would be too low or too high.

Stock-based compensation. We adopted Statement of Financial Accounting Standards No. 123(R), *Share Based Payment*, (SFAS 123(R)) on January 1, 2006 using the modified prospective transition method of implementation and adopted the accelerated attribution method. Prior to January 1, 2006 we followed APB Opinion No. 25, *Accounting for Stock Issued to Employees* (APB 25), and related interpretations, in accounting for our stock-based compensation plans, rather than the alternative fair value accounting method provided for under SFAS No. 123, *Accounting for Stock-Based Compensation*.

We currently use the Black-Scholes-Merton option pricing model to determine the fair value of stock options. The determination of the fair value of stock options 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 the expected stock price volatility over the expected term of the awards, actual and projected employee stock option exercise behaviors, risk-free interest rate and expected dividends. Expected volatility rates are based on historical volatility of the common stock of comparable entities and other factors due to the lack of historic information of the

Company s publicly traded common stock. The expected term of options granted is based on the transition approach provided by Staff Accounting Bulletin (SAB) No. 107 as the options meet the plain vanilla criteria required by this method. The risk-free interest rates are based on the U.S. Treasury yield for a period consistent with the expected term of the option in effect at the time of the grant. We have not paid dividends to our stockholders since the inception and do not plan to pay dividends in the foreseeable future. The stock-based compensation expense for a period is also affected by expected forfeiture

rate for the respective option grants. If our estimates of the fair value of these equity instruments or expected forfeitures are too high or too low, it would have the effect of overstating or understating expenses.

Total stock-based compensation expense, related to all of the Company s stock-based awards, recognized under SFAS 123(R) for the years ended December 31, 2008, 2007, 2006 and recognized for the period from March 13, 2003 (inception) to December 31, 2008, was comprised of the following:

	Year Ended December 31,			Period from March 13, 2003 (Inception) to December 31,
	2008	2007	2006	2008
Research and development	$ 1,748,000	$ 4,259,000	$ 742,000	$ 7,540,000
General and administrative	11,667,000	15,228,000	5,350,000	36,635,000
Total stock-based compensation expense	$ 13,415,000	$ 19,487,000	$ 6,092,000	$ 44,175,000

Recent Accounting Pronouncements

In December 2007, the FASB issued SFAS No. 141(R), a revision of SFAS No. 141, *Business Combinations.* The revision is intended to simplify existing guidance and converge rulemaking under U.S. generally accepted accounting principles with international accounting standards. This statement applies prospectively to business combinations where the acquisition date is on or after the beginning of the first annual reporting period beginning on or after December 15, 2008. Early adoption is prohibited. The implementation of this standard will not have a material impact on our consolidated financial position and results of operations.

In June 2008, the FASB issued FSP EITF 03-6-1, Determining Whether Instruments Granted in Share-Based Payment Transactions Are Participating Securities (FSP EITF 03-6-1). FSP EITF 03-6-1 clarified that all outstanding unvested share-based payment awards that contain rights to nonforfeitable dividends participate in undistributed earnings with common shareholders. Awards of this nature are considered participating securities and the two-class method of computing basic and diluted earnings per share must be applied. FSP EITF 03-6-1 is effective for fiscal years beginning after December 15, 2008. The implementation of this standard will not have a material impact on our consolidated financial position and results of operations.

In November 2008, the FASB ratified EITF Issue No. 08-6, Equity method Investment Accounting Considerations (EITF 08-6). EITF 08-6 addresses a number of matters associated with the impact of SFAS No. 141R and SFAS No. 160 on the accounting for equity method investments including initial recognition and measurement and subsequent measurement issues. EITF 08-6 is effective, on a prospective basis, for fiscal years beginning after December 15, 2008 and interim periods within those fiscal years. The implementation of this standard will not have a material impact on our consolidated financial position and results of operations.

Results of operations

We have a limited history of operations. We anticipate that our results of operations will fluctuate for the foreseeable future due to several factors, including any possible payments made or received pursuant to licensing or collaboration

agreements, progress of our research and development efforts, and the timing and outcome of clinical trials and related possible regulatory approvals. Our limited operating history makes predictions of future operations difficult or impossible. Since our inception, we have incurred significant losses. As of December 31, 2008, we had a deficit accumulated during the development stage of approximately $225.0 million. We anticipate incurring additional losses for the foreseeable future, and these losses may be incurred at increasing rates.

Year ended December 31, 2008 compared to year ended December 31, 2007

Research and development expenses. Research and development expenses decreased by approximately $23.3 million, or 49%, to approximately $23.9 million for the year ended December 31, 2008 compared to approximately $47.2 million for the year ended December 31, 2007.

The following table discloses the components of research and development expenses reflecting all of our project expenses for the years ended December 31, 2008 and 2007:

Research and Development Expenses	Year Ended December 31, 2008	2007
Direct project costs:		
Clinical trials	$ 7,441,000	$ 14,595,000
Contract research and development, consulting, materials and other direct costs	8,731,000	16,253,000
Milestone license fees		6,000,000
Salaries, benefits and related costs	4,089,000	4,007,000
Stock-based compensation	1,748,000	4,259,000
Total direct costs	22,009,000	45,114,000
Indirect project costs	1,926,000	2,121,000
Total	$ 23,935,000	$ 47,235,000

Direct costs decreased by approximately $23.1 million primarily as a result of the absence of any milestone license payments in 2008, lower expenses relating to our NDA for iloperidone and lower clinical trial and manufacturing expenses and by decreases in stock-based compensation expense. Clinical trials expense decreased by approximately $7.2 million primarily due to the costs incurred in 2007 in our Phase III trial of iloperidone in schizophrenia and in our tasimelteon clinical pharmacology trials that were completed in 2007. The clinical trial costs incurred in 2008 relate primarily to our Phase III trial of tasimelteon in primary insomnia that we initiated during the third quarter of 2007. Contract research and development, consulting, materials and other direct costs decreased by approximately $7.5 million primarily as a result of decreased development costs incurred in connection with the lower manufacturing costs for the iloperidone and tasimelteon programs netted with the increase in consulting fees incurred with the engagement of the regulatory consultant to assist us in our efforts to obtain FDA approval of the iloperidone NDA. Prior to FDA approval of our products, manufacturing related costs are included in research and development expense. There were no milestone license fees incurred in 2008. Stock-based compensation expense decreased by approximately $2.5 million as a result of the lower fair value of options granted during 2008 compared to options granted in prior periods and the reversal of cumulative amortization of deferred stock-based compensation related to the cancellation of unvested options in connection with the workforce reduction in December 2008.

General and administrative expenses. General and administrative expenses decreased related to approximately $3.9 million, or 12%, to approximately $28.9 million for the year ended December 31, 2008 from approximately $32.8 million for the year ended December 31, 2007.

The following table analyzes the components of our general and administrative expenses for the years ended December 31, 2008 and 2007:

General and Administrative Expenses	Year Ended December 31, 2008	2007

Salaries, benefits and related costs	$ 4,946,000	$ 3,263,000
Stock-based compensation	11,667,000	15,228,000
Marketing and related consulting services	5,731,000	8,047,000
Legal and other professional expenses	3,719,000	3,142,000
Other expenses	2,847,000	3,124,000
Total	$ 28,910,000	$ 32,804,000

Salaries, benefits and related costs increased by approximately $1.7 million for the year ended December 31, 2008 due to a severance accrual of $1.0 million relating to the workforce reduction in December

2008. Stock-based compensation expense decreased by approximately $3.6 million as a result of the reversal of cumulative amortization of deferred stock-based compensation related to the cancellation of unvested options in connection with the workforce reduction in December 2008 and to the lower fair value of options granted during 2008 compared to options granted in prior periods. Marketing and related consulting services decreased by approximately $2.3 million due to the decrease in our market research and other pre-commercial launch activities following receipt of the not-approvable letter from the FDA regarding the Company s NDA for iloperidone. Legal and other professional expenses increased by approximately $577,000 due primarily to a higher level of consulting activity in 2008 in support of business development activities. Other expenses decreased approximately $277,000 primarily due to lower accounting fees relating to compliance with the Sarbanes-Oxley Act (Sarbanes-Oxley). The 2007 accounting fees for Sarbanes-Oxley were higher due to the first year implementation for the Company to be compliant with Sarbanes-Oxley.

Other income, net. Net other income for the year ended December 31, 2008 was approximately $1.8 million compared to approximately $6.0 million for the year ended December 31, 2007. Interest income decreased by approximately $4.1 million due to lower average cash and marketable securities balances for the year and lower short-term interest rates which generated substantially lower interest income than in 2007. Other income for the year ended December 31, 2007 includes approximately $71,000 in revenue recognized from a grant from the Economic Development Board in Singapore. We do not expect to receive similar grants in the future.

The following table analyzes the components of our other income, net amounts:

	Year Ended December 31,	
	2008	**2007**
Interest income	$ 1,781,000	$ 5,907,000
Other income		71,000
Total, net	$ 1,781,000	$ 5,978,000

Year ended December 31, 2007 compared to year ended December 31, 2006

Research and development expenses. Research and development expenses decreased by approximately $4.8 million, or 9.3%, to approximately $47.2 million for the year ended December 31, 2007 compared to approximately $52.1 million for the year ended December 31, 2006.

The following table discloses the components of research and development expenses reflecting all of our project expenses for the years ended December 31, 2007 and 2006:

	Year Ended December 31,	
Research and Development Expenses	**2007**	**2006**
Direct project costs:		
Clinical trials	$ 14,595,000	$ 36,249,000
Contract research and development, consulting, materials and other costs	16,253,000	8,958,000

Milestone license fees	6,000,000	1,000,000
Salaries, benefits and related costs	4,007,000	3,327,000
Stock-based compensation	4,259,000	742,000
Total direct costs	45,114,000	50,276,000
Indirect project costs	2,121,000	1,795,000
Total	$ 47,235,000	$ 52,071,000

Direct costs decreased by approximately $5.2 million primarily as a result of lower clinical trial expenses for the Company s iloperidone and tasimelteon Phase III trials that were primarily completed in 2006, offset

by increase in clinical manufacturing activities for both iloperidone and tasimelteon and by increases in milestone license fees and stock-based compensation expense. Clinical trials expense decreased by approximately $21.7 million primarily due to the costs incurred in 2006 in our Phase III trial of iloperidone in schizophrenia and in our Phase III trial of tasimelteon in transient insomnia that were completed primarily in 2006. The clinical trial costs incurred in 2007 relate primarily to our Phase II trial of VSF-173 in excessive sleepiness, to our Phase III trial of tasimelteon in chronic insomnia that we initiated during the fourth quarter of 2007, and to the completion of our Phase III trial of iloperidone in schizophrenia. Contract research and development, consulting, materials and other direct costs increased by approximately $7.3 million primarily as a result of increased NDA related expenses and development costs incurred in connection with the manufacturing of clinical supply materials for our iloperidone and tasimelteon programs. Prior to FDA approval of our products, manufacturing related costs are included in research and development expense. Milestone license fees increased by $5.0 million due to the milestone license fee payment to Novartis during 2007 upon the acceptance of our NDA filing for iloperidone during 2007. Salaries, benefits and related costs increased approximately $680,000 for the year ended December 31, 2007 due to an increase in personnel to support the development and clinical trial activities for iloperidone and tasimelteon. Stock-based compensation expense increased by approximately $3.5 million as a result of the higher fair value of options granted during 2007 compared to options granted in prior periods.

General and administrative expenses. General and administrative expenses increased approximately $19.2 million, or 141%, to approximately $32.8 million for the year ended December 31, 2007 from approximately $13.6 million for the year ended December 31, 2006.

The following table analyzes the components of our general and administrative expenses for the years ended December 31, 2007 and 2006:

	Year Ended December 31,	
General and Administrative Expenses	**2007**	**2006**
Salaries, benefits and related costs	$ 3,263,000	$ 2,609,000
Stock-based compensation	15,228,000	5,350,000
Marketing and related consulting services	8,047,000	1,187,000
Legal and other professional expenses	3,142,000	1,760,000
Other expenses	3,124,000	2,732,000
Total	$ 32,804,000	$ 13,638,000

Salaries, benefits and related costs increased by approximately $654,000 for the year ended December 31, 2007 due to an increase in personnel as we continued to develop the administrative, market research, business development and other functions required to support the development and clinical trial activities for iloperidone, tasimelteon and our other product candidates. Stock-based compensation expense increased by approximately $9.9 million as a result of the higher fair value of options granted during 2007 compared to options granted in prior periods. Marketing and related consulting services increased by approximately $6.9 million due to the increase in our market research and other pre-commercial launch activities. Legal and other professional expenses increased by approximately $1.4 million due primarily to an increase in legal, accounting and other professional expenses associated with being a public company as well as due to a higher level of consulting activity in 2007 in support of business development activities. Other expenses increased approximately $392,000 primarily due to increased insurance costs.

Other income, net. Net other income in the year ended December 31, 2007 was approximately $6.0 million compared to net other income of approximately $2.2 million in the year ended December 31, 2006. Interest income increased by approximately $3.7 million due to higher average cash and marketable securities balances for the year and higher short-term interest rates which generated substantially higher interest income than in 2006. Other income for the year ended December 31, 2007 includes approximately $71,000 in revenue recognized from a grant from the Economic Development Board in Singapore. We do not expect to receive similar grants in the future.

Our other income, net for the years ended December 31, 2007 and 2006 are as follows:

	Year Ended December 31,	
	2007	2006
Interest income	$ 5,907,000	$ 2,203,000
Interest expense		(5,000)
Other income	71,000	
Total, net	$ 5,978,000	$ 2,198,000

Liquidity and capital resources

We have funded our operations through December 31, 2008 principally with the net proceeds from private preferred stock offerings totaling approximately $62.0 million, with net proceeds from our April 2006 initial public offering of approximately $53.3 million and with net proceeds from our January 2007 follow-on offering of approximately $111.3 million.

At December 31, 2008, our total cash and cash equivalents and marketable securities were approximately $46.5 million, compared to approximately $93.2 million at December 31, 2007. Our cash and cash equivalents are deposits in operating accounts and highly liquid investments with an original maturity of 90 days or less at date of purchase and consist of time deposits, investments in money market funds with commercial banks and financial institutions, and commercial paper of high-quality corporate issuers.

As of December 31, 2008 and 2007 our liquidity resources are summarized as follows:

	As of December 31,	
	2008	2007
Balance sheet data		
Cash and cash equivalents	$ 39,079,000	$ 41,930,000
U.S. Treasury and government agencies	2,000,000	3,980,000
U.S. corporate debt	5,252,000	33,339,000
U.S. asset-backed securities	127,000	5,925,000
Marketable securities, short-term	7,379,000	43,244,000
U.S. Treasury and government agencies		2,002,000
U.S. corporate debt		1,970,000
U.S. asset-backed securities		4,007,000
Marketable securities, long-term		7,979,000
	$ 46,458,000	$ 93,153,000

As of December 31, 2008, we maintained all of our cash, cash equivalents and marketable securities in three financial institutions. Deposits held with these institutions may exceed the amount of insurance provided on such deposits, but we do not anticipate any losses with respect to such deposits.

In September 2006, the FASB issued Statement No. 157, Fair Value Measurements (SFAS 157). SFAS 157 defines fair value, establishes a framework for measuring fair value in accordance with GAAP, and expands disclosures about fair value measurements. In February 2008, the FASB agreed to delay the effective date of SFAS 157 for all nonfinancial assets and nonfinancial liabilities, except those that are recognized or disclosed at fair value in the financial statements on a recurring basis, to fiscal years beginning after November 15, 2008. The Company has adopted the provisions of SFAS 157 as of January 1, 2008, for financial instruments. Although the adoption of SFAS 157 did not materially impact its financial condition, results of operations, or cash flow, the Company is now required to provide additional disclosures as part of its financial statements. Under FAS No. 159, entities are permitted to choose to measure many financial instruments and certain other items at fair value. The Company did not elect the fair value measurement

option under FAS No. 159, The Fair Value Option for Financial Assets and Financial Liabilities including an amendment to FAS 115 (SFAS 159), for any of its financial assets or liabilities.

SFAS 157 establishes a three-tier fair value hierarchy, which prioritizes the inputs used in measuring fair value. These tiers include:

Level 1 defined as observable inputs such as quoted prices in active markets

Level 2 defined as inputs other than quoted prices in active markets that are either directly or indirectly observable

Level 3 defined as unobservable inputs in which little or no market data exists, therefore requiring an entity to develop its own assumptions

As of December 31, 2008, the Company held certain assets that are required to be measured at fair value on a recurring basis. The Company currently does not have non-financial assets and non-financial liabilities that are required to be measured at fair value on a recurring basis.

	Fair Value Measurements at Reporting Date Using		
	Quoted Prices in Active Markets for Identical Assets	**Significant Other Observable Inputs**	**Significant**