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 u