Vanda Pharmaceuticals Inc.
Form 10-K
February 26, 2013
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UNITED STATES SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

Form 10-K

þ **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

For the fiscal year ended December 31, 2012

¨ **TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**

Commission File No. 001-34186

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.)*

2200 Pennsylvania Avenue NW, Suite 300 E

Washington D.C. 20037

(202) 734-3400

(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 ¨ 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 ¨ 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 ¨

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes þ No ¨

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

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

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

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 ¨ No þ

As of June 29, 2012, the aggregate market value of the Common Stock held by non-affiliates of the registrant was approximately $106.2 million based on the closing price of the registrant s Common Stock, as reported by the NASDAQ Global Market, 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 February 20, 2013 was 28,342,659.

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

Specified portions of the registrant s proxy statement with respect to the registrant s 2013 Annual Meeting of Stockholders, which is to be filed pursuant to Regulation 14A within 120 days after the end of the registrant s fiscal year ended December 31, 2012, are incorporated by reference into Part III of this Form 10-K.

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PART I

CAUTIONARY NOTE REGARDING FORWARD-LOOKING STATEMENTS

Various statements throughout this report are forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995. Forward-looking statements may appear throughout this report. Words such as, but not limited to, believe, expect, anticipate, estimate, intend, plan, project, target, goal, likely, will, would, and could, or the negative of these terms and similar expressions or words, forward-looking statements. Forward-looking statements are based upon current expectations that involve risks, changes in circumstances, assumptions and uncertainties. Important factors that could cause actual results to differ materially from those reflected in our forward-looking statements include, among others:

- the inability to reach agreement with the U.S. Food and Drug Administration regarding our regulatory approval strategy or proposed path to approval for tasimelteon for the treatment of Non-24-Hour Disorder (Non-24);
- the failure to obtain regulatory approval for our products or product candidates, particularly tasimelteon for the treatment of Non-24, or to comply with ongoing regulatory requirements;
- a loss of rights to develop and commercialize our products, product candidates or partnered products under our license and sublicense agreements.
- our failure to develop or obtain sales, marketing and distribution resources and expertise or to otherwise manage our growth;
- the extent and effectiveness of the development, sales and marketing and distribution support Fanapt® receives;
- our ability to successfully commercialize Fanapt® outside of the U.S. and Canada;
- delays in the completion of our or our partners clinical trials;
- a failure of our products, product candidates or partnered products to be demonstrably safe and effective;
- a lack of acceptance of our products, product candidates or partnered products in the marketplace, or a failure to become or remain profitable;
- our expectations regarding trends with respect to our revenues, costs, expenses and liabilities;
- our inability to obtain the capital necessary to fund our research and development or commercial activities;
- our failure to identify or obtain rights to new products or product candidates;

limitations on our ability to utilize some or all of our prior net operating losses and research and development credits;

a loss of any of our key scientists or management personnel; and

losses incurred from product liability claims made against us.

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 management s discussion and analysis of our financial condition and results of operations and our consolidated financial statements contained in this annual report on Form 10-K. We also encourage you to read Item 1A of Part 1 of this annual report on Form 10-K, 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. Therefore, the information in this report should be read together with other reports and documents that

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we file with the Securities and Exchange Commission (SEC) from time to time, including on Form 10-Q and Form 8-K, which may supplement, modify, supersede or update those risk factors. 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

Vanda Pharmaceuticals Inc. (we, Vanda or the Company) is a biopharmaceutical company focused on the development and commercialization of products for the treatment of central nervous system disorders. We believe that each of our products and partnered products will address markets with significant unmet medical needs. Our product portfolio includes tasimelteon, a compound for the treatment of circadian rhythm sleep disorders (CRSD), which is currently in clinical development for Non-24, Fanapt®, a compound for the treatment of schizophrenia, the oral formulation of which is currently being marketed and sold in the U.S. by Novartis Pharma AG (Novartis), and VLY-686, a small molecule neurokinin-1 receptor (NK-1R) antagonist.

Throughout this annual report on Form 10-K, we refer to Fanapt® within the U.S. and Canada as our partnered product and we refer to Fanapt® outside the U.S. and Canada, tasimelteon and VLY-686 as our products. All other compounds are referred to herein as our product candidates. In addition, we refer to our partnered products, products and product candidates collectively as our compounds. Moreover, we refer to drug products generally as drugs or products.

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 compounds. Our ability to generate revenue and achieve profitability largely depends on our ability, alone or with others, to complete the development of our products or product candidates, and to obtain the regulatory approvals for and manufacture, market and sell our products and product candidates, including tasimelteon for the treatment of Non-24-Hour Disorder (Non-24) and Novartis ability to successfully commercialize Fanapt® in the U.S. 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 annual report on Form 10-K, entitled Risk Factors.

Our activities will necessitate significant uses of working capital throughout 2013 and beyond. We are currently concentrating our efforts on the development of tasimelteon for the treatment of Non-24 and the preparation of a New Drug Application (NDA) for tasimelteon for the treatment of Non-24 that we plan to file with the U.S. Food and Drug Administration (FDA) in mid-2013. Additionally, we and our partners continue to pursue market approval of Fanapt® in a number of foreign jurisdictions, with Israel and Argentina having already approved Fanapt® for the treatment of schizophrenia.

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. 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.

Our products target prescription markets with significant unmet medical needs. We believe that tasimelteon may represent an important new treatment option for patients with CRSDs based on its potential to be the first compound approved as a circadian regulator with a demonstrated ability to reset the master body clock and align it to a constant 24-hour day. We believe that Fanapt® may address some of the shortcomings of other currently available drugs, based on its observed safety profile.

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Our strategy

Our goal is to create a leading biopharmaceutical company focused on developing and commercializing products that address critical unmet medical needs relating to central nervous system disorders 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 products and product candidates. We believe that Vanda has built a team of capable drug developers that can take products through the development and regulatory processes towards our goal of regulatory approval in markets across the world. In markets where we do not have local expertise, we will leverage partners or consultants to assist towards us.

Establish our capability to commercialize products. We intend to establish a commercial capability to market our products in certain indications and geographies. Vanda has begun to hire experienced sales and marketing professionals to enable the commercialization of our products.

Enter into partnerships to supplement our capabilities and to extend our commercial reach. We intend to build commercial relationships to both supplement our capabilities in markets where we lead commercialization and to make our products available in markets where we do not intend to lead commercialization.

Apply our pharmacogenetics and pharmacogenomics expertise to differentiate our products and product candidates. We believe that our pharmacogenetics and pharmacogenomics expertise will yield new insights into our products and product candidates. These insights may enable us to target our products and product candidates to certain patient populations and to identify unexpected conditions for our products and 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 the acquisition of additional clinical-stage compounds.

Products and partnered products

We have the following products and partnered products on the market or in clinical development:

Product or Partnered Product	Target Indications	Select Milestones
Tasimelteon	Circadian Rhythm Sleep Disorders	Phase III trial (SET Study) for Non-24 completed in December 2012;
		Phase III trial (RESET Study) for Non-24 completed in January 2013;
		Two ongoing open label safety studies
	Major Depressive Disorder (MDD)	Phase IIb/III trial (MAGELLAN) completed in January 2013
	Insomnia	Phase III trial for transient insomnia completed in 2006;
		Phase III trial for chronic primary insomnia completed in 2008
Fanapt® (Oral)	Schizophrenia	FDA approval in May 2009;

		Commercial rights in the U.S. and Canada sublicensed to Novartis in October 2009;
Fanapt® (Injectable)	Schizophrenia	Launched in the U.S. by Novartis in January 2010 Phase II trial initiated by Novartis in 2011; Novartis has ceased the further clinical development of this formulation

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Tasimelteon

Tasimelteon is a circadian regulator in development for the treatment of Non-24. Tasimelteon is a melatonin agonist of the human MT1 and MT2 receptors, with greater specificity for MT2. Tasimelteon s ability to reset the master body clock in the suprachiasmatic nucleus (SCN), located in the hypothalamus, results in the entrainment of the body s melatonin and cortisol rhythms to align to the 24-hour day-night cycle. In December 2012 and January 2013, we announced positive results for two Phase III studies for tasimelteon in the treatment of Non-24. The SET Phase III study demonstrated that tasimelteon was able to entrain the master body clock as measured by melatonin and cortisol circadian rhythms. Tasimelteon was also shown to significantly improve clinical symptoms across a number of sleep and wake measures. These results provided robust evidence of direct and clinically meaningful benefits to patients with Non-24. The RESET Phase III study demonstrated the maintenance effect of 20 milligrams (mg) of tasimelteon to entrain melatonin and cortisol circadian rhythms in individuals with Non-24. Patients treated with tasimelteon maintained their clinical benefits while patients receiving placebo showed significant deterioration in measures of nighttime sleep, daytime naps and timing of sleep. The tasimelteon Non-24 program continues towards its goal of a projected mid-2013 NDA filing with the FDA. We will meet with the FDA in the first quarter of 2013 for a pre-NDA meeting on tasimelteon in the treatment of patients with Non-24.

In January 2010, the FDA granted orphan drug designation status for tasimelteon in Non-24 in blind individuals without light perception. The FDA grants orphan drug designation to drugs that may provide significant therapeutic advantage over existing treatments and target conditions affecting 200,000 or fewer U.S. patients per year. Orphan drug designation provides potential financial and regulatory incentives, including study design assistance, tax credits, waiver of FDA user fees, and up to seven years of market exclusivity upon marketing approval. In February 2011, the European Medicines Agency (EMA) designated tasimelteon as an orphan medicinal product for the same indication.

Tasimelteon has also been studied in Major Depressive Disorder (MDD) and insomnia.

Therapeutic opportunity

Sleep disorders are segmented into three major categories: primary insomnia, secondary insomnia and CRSDs. 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). CRSDs 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 by the hormones melatonin and cortisol. 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 CRSDs include transient disorders such as jet lag and chronic disorders such as shift work sleep disorder and Non-24. Non-24 is a serious, rare circadian rhythm disorder that affects a majority of totally blind individuals who lack light perception and cannot entrain (reset) their master body clock to the 24-hour day. Based on market research we have conducted with LEK Consulting, we believe that CRSDs represent a significant portion of the market for sleep disorders.

While there are no FDA-approved treatments for CRSDs, 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, Ambien® (zolpidem) by sanofi-aventis (including Ambien CR®), Lunesta® (eszopiclone) by Dainippon Sumitomo Pharma, Sonata® (zaleplon) by Pfizer Inc. and Silenor® (doxepin) by Somaxon 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 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. FDA approved drugs for the treatment of insomnia also include Rozerem® (ramelteon) by Takeda Pharmaceuticals Company Limited, a compound with a mechanism of action

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similar to tasimelteon. The class of melatonin agonists includes Rozerem® (ramelteon) by Takeda Pharmaceuticals Company Limited, Valdoxan® (agemelatine) by Servier, Circadin® (long-acting melatonin) by Neurim Pharmaceuticals and the food supplement melatonin.

Limitations of current treatments

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

We believe that none of the drugs used and approved for sleep disorders, other than Rozerem®, 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 (as is the case in CRSD), 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.

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.

Potential advantages of tasimelteon

We believe that tasimelteon may represent a breakthrough treatment option for patients with CRSDs based on the compound s demonstrated ability to reset the master body clock and align it with the 24-hour day. We believe that tasimelteon is unlikely to be scheduled as a controlled substance by the DEA because Rozerem®, 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. Tasimelteon also appears to be safe and well-tolerated, with no significant side effects or effects on next-day performance.

Overview of Phase III clinical trials for Non-24

In December 2012, we reported positive top-line results in a randomized, double-blind, multi-center, placebo-controlled Phase III trial (SET study) that enrolled 84 patients. Tasimelteon succeeded in the primary endpoint of entrainment of the melatonin (aMT6s) rhythm as compared to placebo. Additionally, tasimelteon demonstrated significant improvements across a number of sleep and wake parameters including measures of total sleep time, nap duration, and timing of sleep. Tasimelteon also showed significant improvements over placebo in the Non-24 Clinical Response Scale (N24CRS) as well as in the Clinical Global Impression of Change (CGI-C), an overall global functioning scale. These results provide robust evidence of a direct and clinically meaningful benefit to patients with Non-24. In the SET study, tasimelteon was demonstrated to be safe and well tolerated. The trial examined 20mg of tasimelteon dosed 30 minutes before bedtime versus placebo. The SET study was an 84 patient randomized, double-masked, placebo-controlled study in patients with Non-24. The primary endpoints for this study were entrainment of the melatonin (aMT6s) rhythm to the 24-hour clock and Clinical Response as measured by entrainment plus a score of greater than or equal to 3 on N24CRS.

In January 2013, we announced positive results for the second Phase III study of tasimelteon for the treatment of Non-24. The RESET study demonstrated the maintenance effect of 20mg of tasimelteon to entrain melatonin and cortisol circadian rhythms in individuals with Non-24. Patients treated with tasimelteon maintained their clinical benefits while patients receiving placebo showed significant deterioration in measures of nighttime sleep, daytime naps, and timing of sleep. The RESET study was a 20 patient randomized withdrawal

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study designed to demonstrate the maintenance effect of 20mg of tasimelteon in the treatment of blind individuals with Non-24. Patients were treated with tasimelteon for three months during an open-label run-in phase. Patients who responded to tasimelteon treatment during the run-in phase, as measured by entrainment of the melatonin rhythm (aMT6s) to the 24-hour day, were then randomized to receive either placebo or continue receiving tasimelteon 20mg for 2 months. The primary endpoint of the study was the maintenance of effect as measured by entrainment of the melatonin (aMT6s) rhythm.

Two open-label safety studies are ongoing for tasimelteon in Non-24. The 3202 and 3204 clinical trials are open-label, multicenter, studies in blind subjects with Non-24 to assess the safety of tasimelteon. The tasimelteon Non-24 program continues towards its goal of a projected mid-2013 NDA filing with the FDA. We will meet with the FDA in the first quarter of 2013 for a pre-NDA meeting on tasimelteon in the treatment of patients with Non-24.

Overview of Phase III clinical trials for insomnia

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 20mg, 50mg and 100mg 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. 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 trial in chronic primary insomnia that enrolled 324 patients. The trial examined tasimelteon at 20mg and 50mg versus placebo over a period of 35 days. The trial measured time to fall asleep and sleep maintenance, as well as next-day performance.

Overview of Phase IIb/ III clinical trials for major depressive disorder

In January 2013, Vanda reported top-line results of the Phase IIb/III clinical study (MAGELLAN) in MDD, investigating the efficacy and safety of tasimelteon as a monotherapy in the treatment of patients with MDD. The clinical study did not meet the primary endpoint of change from baseline in the Hamilton Depression Scale (HAMD-17) after 8 weeks of treatment as compared to placebo. Tasimelteon was shown to be safe and well-tolerated, consistent with observations in prior studies. Based on these proof of concept clinical study results, Vanda decided to discontinue all activities in this indication. MAGELLAN was a proof of concept, two arm (tasimelteon 20mg and placebo), 8-week, double-masked, randomized, phase IIb/III clinical study in patients with MDD. The study enrolled 507 patients in 43 sites in the U.S.

Intellectual property

Tasimelteon and its formulations, genetic markers and uses are covered by a total of 11 patent and patent application families worldwide. The primary new chemical entity patent covering tasimelteon expires normally in 2017 in the U.S. and in most European markets. We believe that, like Fanapt®, tasimelteon will meet the various criteria of the Hatch-Waxman Act and will receive five additional years of patent protection in the U.S., which would extend its new chemical entity patent protection in the U.S. until 2022. In Europe, data exclusivity will protect tasimelteon for at least ten years from approval. Outside the U.S. and Europe, data exclusivity will protect tasimelteon from generic competition for varying number of years depending on the country. Additional patent applications directed to specific sleep disorders and to methods of administration, if issued, would provide exclusivity for such indications and methods of administration. Patent applications directed to the treatment of Non-24, if granted, would provide exclusivity for this indication until at least 2033.

Our rights to the new chemical entity patent covering tasimelteon and related intellectual property have been acquired through a license with Bristol-Myers Squibb Company (BMS). Please see License agreements below for a discussion of this license.

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Fanapt®

Fanapt® is a compound for the treatment of schizophrenia. In May 2009, the FDA granted U.S. marketing approval of Fanapt® for the acute treatment of schizophrenia in adults. On October 2009, we entered into an amended and restated sublicense agreement with Novartis. We had originally entered into a sublicense agreement with Novartis in June 2004 pursuant to which we obtained certain worldwide exclusive licenses from Novartis relating to Fanapt®. Pursuant to the amended and restated sublicense agreement, Novartis has exclusive commercialization rights to all formulations of Fanapt® in the U.S. and Canada. In January 2010, Novartis launched Fanapt® in the U.S. Novartis is responsible for the further clinical development activities in the U.S. and Canada, including the development of a long-acting injectable (or depot) formulation of Fanapt®. In October 2012, Novartis informed us that it had determined to cease the development of the long-acting injectable (or depot) formulation of Fanapt®.

We continue to explore the regulatory path and commercial opportunity for Fanapt® oral formulation outside of the U.S. and Canada. In December 2012, the European Medicines Agency s (EMA) Committee for Medicinal Product for Human Use (CHMP) issued a negative opinion recommending against approval of Fanaptum (oral iloperidone tablets) for the treatment of schizophrenia in adult patients in the European Union. The CHMP was of the opinion that the benefits of Fanaptum did not outweigh its risks and recommended against marketing authorization at this point in time. In January 2013, we formally appealed the EMA s negative opinion and requested a re-examination of the decision by the CHMP. We have entered into agreements with the following partners for the commercialization of Fanapt® in the countries set forth below:

Country	Partner
Mexico	Probiomed S.A. de C.V.
Israel	Megapharm Ltd.

In August 2012, the Israeli Ministry of Health granted market approval for Fanapt® for the treatment of schizophrenia. In November 2012, we were notified, that Fanapt® had been granted market approval in Argentina for the treatment of schizophrenia.

Our rights to the new chemical entity patent covering Fanapt® and related intellectual property have been acquired through a license with Novartis. Please see License agreements below for a discussion of this license.

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. Currently approved atypical antipsychotics include, in addition to Fanapt®, Risperdal® (risperidone), including the depot formulation Risperdal® Consta®, and Invega® (paliperidone), including the depot formulation Invega® Sustenna , each by Ortho-McNeil-Janssen Pharmaceuticals, Inc., Zyprexa® (olanzapine), including the depot formulation Zyprexa® Relprevv , by Eli Lilly and Company, Seroquel® (quetiapine) by AstraZeneca PLC, Abilify® (aripiprazole) by BMS/Otsuka Pharmaceutical Co., Ltd., Geodon® (ziprasidone) by Pfizer Inc., Saphris® (asenapine) by Schering-Plough, Latuda® (lurasidone) by Dainippon Sumitomo Pharma, and generic clozapine.

The long-acting injectable (or depot) formulation of Fanapt® is administered once every four weeks and we believe will be a compelling complement to the 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

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demonstrated the benefit of consistent release over a four-week time period with no greater side effects relative to oral dosing. In October 2012, Novartis informed us that it had determined to cease the development of the depot formulation.

Intellectual property

Fanapt® and its metabolites, formulations, genetic markers and uses are covered by a total of 18 patent and patent application families worldwide. The primary new chemical entity patent covering Fanapt® was set to expire normally in 2011 in the U.S. and expired in 2010 in major markets outside the U.S. In the U.S., 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. Fanapt® has qualified for the full five-year patent term extension and so the term of the new chemical entity patent in the U.S. has been extended until November 2016. In addition, we expect that Fanapt® will be eligible for six months of pediatric exclusivity potentially extending the term of the new chemical entity patent in the U.S. until May 2017. In Europe, statutes provide for ten years of data exclusivity (with the potential for an additional year if the drug is developed for a significant new indication). No generic versions of Fanapt® would be permitted to be marketed or sold during this 10-year (or 11-year) period in most European countries. Consequently, assuming that pediatric exclusivity is granted by the FDA and that we receive regulatory approval in Europe, we expect that Novartis rights to commercialize Fanapt® will be exclusive until May 2017 in the U.S. and our rights to commercialize Fanapt® will be exclusive for at least 10 years from approval in Europe. Outside the U.S. and Europe, data exclusivity will protect Fanapt® from generic competition for varying numbers of years depending upon the country. The patent for the microsphere long-acting injectable (or depot) formulation of Fanapt® expires in 2024 in the U.S. and 2022 in most of the major markets in Europe. The pending patent application for the aqueous microcrystals long acting injectable (or depot) formulation of Fanapt® will expire in 2023 in the U.S. The patent for the aqueous microcrystals long acting injectable (or depot) formulation of Fanapt® will expire in 2023 in most of the major markets in Europe. Several other patent applications covering metabolites, uses, formulations and genetic markers relating to Fanapt® extend beyond 2020.

We acquired worldwide, exclusive rights to the new chemical entity patent covering Fanapt® and certain related intellectual property from Novartis under a sublicense agreement we entered into in 2004, which was amended and restated in 2009. Please see License agreements below for a more complete description of the rights we acquired from and relinquished to Novartis with respect to Fanapt®.

VLY-686

VLY-686 is an NK-1R antagonist that we licensed from Eli Lilly and Company (Lilly) in April 2012. NK-1R antagonists have been evaluated in a number of indications including chemotherapy-induced nausea and vomiting (CINV), post-operative nausea and vomiting (PONV), alcohol dependence, anxiety, depression and pruritus. We are currently examining the clinical and commercial profile of VLY-686. This strategic evaluation will further inform potential indications for an early development clinical program.

Intellectual property

VLY-686 is covered by a total of three patent and patent application families worldwide. The new chemical patent covering VLY-686 expires in April 2023, except in the U.S., where it expires in June 2024 absent any applicable patent term adjustments.

License agreements

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

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

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fee of $0.5 million. We made a milestone payment to BMS of $1.0 million under this license agreement in 2006 relating to the initiation of our first Phase III clinical trial for tasimelteon. We would be obligated to make future milestone payments to BMS and Massachusetts General Hospital (MGH) of less than $40.0 million in the aggregate (the majority of which are tied to sales milestones). In the event that a tasimelteon NDA is accepted for filing by the FDA, we will incur milestone obligations of $3.8 million. Additionally, we would be obligated to make 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 would also be obligated under this license 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.

The license agreement with BMS was amended in May 2012 to, among other things, extend the deadline by which we must enter into a development and commercialization agreement with a third party for tasimelteon until the earliest of: (i) the date mutually agreed upon by BMS and us following the provision by us to BMS of a full written report of the Phase III clinical studies on which we intend to rely for filing for marketing authorization for tasimelteon in its first major market country (Phase III report); (ii) the date of the acceptance by a regulatory authority of the filing by us for marketing authorization for tasimelteon in a major market country following the provision by us to BMS of the Phase III report; or (iii) December 31, 2013.

If we have not entered into a development and commercialization agreement with respect to certain major market countries by the foregoing deadline, then BMS will have the option to exclusively develop and commercialize tasimelteon on its own in those countries not covered by such an agreement on pre-determined financial terms, including milestone and royalty payments. In addition to the foregoing, pursuant to the May 2012 amendment, our deadline for filing an NDA with the FDA for tasimelteon was extended until January 1, 2014.

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.

Fanapt®

We acquired exclusive worldwide rights to patents and patent applications for Fanapt® through a sublicense agreement with Novartis. A predecessor company of sanofi-aventis, Hoechst Marion Roussel, Inc. (HMRI), discovered Fanapt® and completed early clinical work on the compound. In 1996, following a review of its product portfolio, HMRI licensed its rights to the Fanapt® patents and patent applications to Titan Pharmaceuticals, Inc. (Titan) on an exclusive basis. In 1997, soon after it had acquired its rights, Titan sublicensed its rights to Fanapt® on an exclusive basis to Novartis. In June 2004, we acquired exclusive worldwide rights to these patents and patent applications as well as certain Novartis patents and patent applications to develop and commercialize Fanapt® through a sublicense agreement with Novartis.

In October 2009, we entered into an amended and restated sublicense agreement with Novartis which amended and restated our June 2004 sublicense agreement with Novartis relating to Fanapt®. Pursuant to the amended and restated sublicense agreement, Novartis has exclusive commercialization rights to all formulations of Fanapt® in the U.S. and Canada. Novartis began selling Fanapt® in the U.S. during the first quarter of 2010. Novartis is responsible for the further clinical development activities in the U.S. and Canada, including the development of a long-acting injectable (or depot) formulation of Fanapt®. In October 2012, Novartis informed us that it had determined to cease the development of the long-acting injectable (or depot) formulation of Fanapt®. Pursuant to the amended and restated sublicense agreement, we received an upfront payment of $200.0 million and are eligible for additional payments totaling up to $265.0 million upon the achievement of certain commercial and development milestones for Fanapt® in the U.S. and Canada. Based on the current sales performance of Fanapt® in the U.S. and the decision by Novartis to cease development of the long-acting injectable (or depot) formulation of Fanapt®, we expect that some or all of these commercial and development

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milestones will not be achieved by Novartis. We also receive royalties, which, as a percentage of net sales, are in the low double-digits, on net sales of Fanapt® in the U.S. and Canada. We retain exclusive rights to Fanapt® outside the U.S. and Canada and we have exclusive rights to use any of Novartis data for Fanapt® for developing and commercializing Fanapt® outside the U.S. and Canada. At Novartis option, we will enter into good faith discussions with Novartis relating to the co-commercialization of Fanapt® outside of the U.S. and Canada or, alternatively, Novartis will receive a royalty on net sales of Fanapt® outside of the U.S. and Canada.

We may lose our rights to develop and commercialize Fanapt® outside the U.S. and Canada if we fail to comply with certain requirements in the amended and restated sublicense agreement regarding our financial condition, or if we fail to comply with certain diligence obligations regarding our development or commercialization activities or if we otherwise breach the amended and restated sublicense agreement and fail to cure such breach. Our rights to develop and commercialize Fanapt® outside the U.S. and Canada may be impaired if we do not cure breaches by Novartis of similar obligations contained in its sublicense agreement with Titan for Fanapt®. In addition, if Novartis breaches the amended and restated sublicense agreement with respect to its commercialization activities in the U.S. or Canada, we may terminate Novartis commercialization rights in the applicable country and we would no longer receive royalty payments from Novartis in connection with such country in the event of such termination.

VLY-686

In April 2012, we entered into a license agreement with Lilly pursuant to which we acquired an exclusive worldwide license under certain patents and patent applications, and other licenses to intellectual property, to develop and commercialize an NK-1R antagonist, VLY-686, for all human indications.

Pursuant to the agreement, we paid Lilly an initial license fee of $1.0 million and we will be responsible for all development costs. Lilly is also eligible to receive additional payments based upon achievement of specified development and commercialization milestones as well as tiered-royalties on net sales at percentage rates up to the low double digits. These milestones include $4.0 million for pre-NDA approval milestones and up to $95.0 million for future regulatory approval and sales milestones. We have agreed to use commercially reasonable efforts to develop and commercialize VLY-686.

Either party may terminate the agreement under certain circumstances, including a material breach of the agreement by the other. In the event that we terminate the agreement, or if Lilly terminates the agreement due to our breach or for certain other reasons set forth in the agreement, all rights licensed and developed by us under the agreement will revert or otherwise be licensed back to Lilly on an exclusive basis, subject to payment by Lilly to us of a royalty on net sales of products that contain VLY-686.

Government regulation

Government authorities in the U.S., 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 products. Other than Fanapt® in the U.S., Israel and Argentina, all of our compounds 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 U.S., the FDA regulates drugs under the Federal Food, Drug and Cosmetic Act, as amended, 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.

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The steps required before a drug may be marketed in the U.S. 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 drug 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 drug is produced to assess compliance with Current Good Manufacturing Practices (cGMP); and
- 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 drug. 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 U.S., 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 U.S. 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 drug warrants further clinical trials based on preliminary indications of efficacy. These pilot studies may be performed in the U.S. after an IND has become effective or outside of the U.S. prior to the filing of an IND in the U.S. in accordance with applicable government regulations and institutional procedures.

Clinical trials involve the administration of the investigational new drug 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 healthy 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 drug 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 new 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.

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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 U.S. 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 drug 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, we or our partners 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 drug 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.

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 drug, to the FDA, in the form of an NDA, requesting approval to market the drug 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 drug is safe and effective for its intended use.

Before approving an NDA, the FDA will inspect the facility or facilities where the drug 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 issue complete response letter (CRL), in which 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.

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 or our partners may encounter difficulties or unanticipated costs in our efforts to secure necessary governmental approvals, which could delay or preclude us or our partners from marketing our products or partnered products or product candidates. Furthermore, the FDA may prevent a drug developer from marketing a drug 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 drug. After approval, some types of changes to the approved drug, 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 within countries outside the U.S.

If the FDA approves the NDA, the drug becomes available for physicians to prescribe in the U.S. After approval of our products or partnered products or product candidates, we 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 and our partners also are 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

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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 drug 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 or our partners may have to conduct other trials and studies to explore use of the approved product 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 product or partnered product and its acceptance in the medical community.

We use, and will continue to use, third-party manufacturers to produce our products and product candidates 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.

In September 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 made 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 changed 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 made certain changes to the user fee provisions to permit the use of user fee revenue to fund the FDA s drug product safety activities and the review of Direct-to-Consumer advertisements. The Food and Drug Administration Safety and Innovation Act of 2012, which became effective in October 2012, reauthorized the authority of the FDA to collect user fees to fund the FDA s review activities.

In addition, new government requirements may be established that could delay or prevent regulatory approval of our products and product candidates 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 drug. 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 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, 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 drug 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 drug. A certification that the new drug will not infringe the already approved drug 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 drug have expired.

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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 drug 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 drug 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 or our partners obtain FDA approval for a product or product candidate, we must obtain approval by the comparable regulatory authorities of foreign countries before we can commence clinical trials or marketing of the product or product candidate 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 U.S. 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 MAAs either under a centralized or decentralized procedure. The centralized procedure, which is available for drugs 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 U.S. We face the risk that the resulting prices would be insufficient to generate an acceptable return to us or our partners.

Third-party reimbursement and pricing controls

In the U.S. 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 or our partners to go through the process of seeking reimbursement from Medicare and private payors. Our compounds may not be considered cost-effective, and coverage and reimbursement may not be available or sufficient to allow us or our partners to sell our compounds on a competitive and profitable basis. The passage of the Medicare Prescription Drug and Modernization Act of 2003 imposes additional requirements for the distribution and pricing of prescription drugs which may affect the marketing of our compounds.

In many foreign markets, including the countries in the European Union and Japan, pricing of pharmaceutical products is subject to governmental control. In the U.S., there have been, and we expect that there

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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.

Marketing and sales

Given the range of potential indications for tasimelteon, we may pursue one or more partnerships for the development and commercialization of tasimelteon worldwide.

In October 2009, we entered into an amended and restated sublicense agreement with Novartis pursuant to which Novartis has exclusive commercialization rights to all formulations of Fanapt® in the U.S. and Canada. Novartis began selling Fanapt® in the U.S. during the first quarter of 2010.

We continue to explore the regulatory path and commercial opportunity for Fanapt® oral formulation outside of the U.S. and Canada. In December 2012, the CHMP issued a negative opinion recommending against approval of Fanaptum (oral iloperidone tablets) for the treatment of schizophrenia in adult patients in the European Union. The CHMP was of the opinion that the benefits of Fanaptum did not outweigh its risks and recommended against marketing authorization at this point in time. In January 2013, we formally appealed the EMA s negative opinion and requested a re-examination of the decision by the CHMP. We have entered into agreements with the following partners for the commercialization of Fanapt® in the countries set forth below:

Country	Partner
Mexico	Probiomed S.A. de C.V.
Israel	Megapharm Ltd.

In August 2012, the Israeli Ministry of Health granted market approval for Fanapt® for the treatment of schizophrenia. In November 2012, we were notified that Fanapt® had been granted market approval in Argentina for the treatment of schizophrenia.

Patents and proprietary rights; Hatch-Waxman protection

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

Fanapt®, tasimelteon and VLY-686 are covered by new chemical entity and other patents. These patents cover the active pharmaceutical ingredient and provide patent protection for all formulations containing these active pharmaceutical ingredients. The new chemical entity patent for Fanapt® is owned by sanofi-aventis, and other patents and patent applications relating to Fanapt® are owned by Novartis. BMS owns the new chemical entity patent for tasimelteon and Lilly owns the new chemical entity patent for VLY-686. We originally obtained exclusive worldwide rights to develop and commercialize the compounds covered by these patents through license and sublicense arrangements. However, pursuant to the amended and restated sublicense agreement with Novartis, Novartis obtained exclusive commercialization rights to all formulations of Fanapt® in the U.S. and Canada. 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 Fanapt® and tasimelteon.

The new chemical entity patent covering Fanapt® was set to expire normally in 2011 in the U.S. and expired in 2010 in major markets outside of the U.S. The new chemical entity patent covering tasimelteon expires in 2017 in the U.S. and most European markets. The new chemical entity patent covering VLY-686 expires in April 2023, except in the U.S., where it expires in June 2024 absent any applicable patent term adjustments. Additionally, Fanapt® has qualified for the full five-year patent term extension and so the term of the new chemical entity patent in the U.S. has been extended until November 2016. A similar extension is expected to be available for tasimelteon and may also be available for VLY-686. Fanapt® will also be eligible for 6 months of additional protection for completing studies in the pediatric population potentially extending the term of the new

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chemical entity parent in the U.S. until May 2017. These studies, for which Novartis is responsible, are required by the FDA approval letter. In Europe, statutes provide for ten years of data exclusivity, with the potential for an additional year if the company develops the drug for a significant new indication. No generic versions of Fanapt® would be permitted to be marketed or sold during this 10-year (or 11-year) period in most European countries. Consequently, assuming that pediatric exclusivity is granted by the FDA and that we receive regulatory approval in Europe, we expect that Novartis rights to commercialize Fanapt® will be exclusive until May 2017 in the U.S. and our rights in Europe would be exclusive for at least 10 years from approval in Europe. Data exclusivity periods in other countries vary from country to country. The patent for the microsphere long-acting injectable (or depot) formulation of Fanapt® expires in 2024 in the U.S. and 2022 in most of the major markets in Europe. The pending patent application for the aqueous microcrystals long acting injectable (or depot) formulation of Fanapt® will expire in 2023 in the U.S. The patent for the aqueous microcrystals long acting injectable (or depot) formulation of Fanapt® will expire in 2023 in most of the major markets in Europe. Several other patent applications covering metabolites, uses, formulations and genetic markers relating to Fanapt® extend beyond 2020.

Aside from the new chemical entity patents and other in-licensed patents relating to Fanapt®, tasimelteon and VLY-686, as of December 31, 2012 we had 29 patent and patent application families, most of which have been filed in key markets including the U.S., relating to Fanapt® and tasimelteon. In addition, we had five other patent applications relating to compounds not presently in clinical studies. The claims in these various patents and patent applications are directed to compositions of matter, including claims covering other product candidates, pharmaceutical compositions 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 generally 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.

Research and Development

We have built a research and development organization that includes extensive expertise in the scientific disciplines of pharmacogenetics and pharmacogenomics. We operate cross-functionally and are led by an experienced research and development management team. We use rigorous project management techniques to assist us in making disciplined strategic research and development program decisions and to help limit the risk profile of our product pipeline. We also access relevant market information and key opinion leaders in creating target product profiles and, when appropriate, as we advance our programs towards commercialization. We engage third parties to conduct portions of our preclinical research. In addition, we utilize multiple clinical sites to conduct our clinical trials; however we are not substantially dependent upon any one of these sites for our clinical trials nor do any of them conduct a major portion of our clinical trials.

We incurred $45.4 million, $29.0 million and $12.3 million in research and development expenses in the years ended December 31, 2012, 2011 and 2010, respectively.

Manufacturing

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

We intend to rely on third-party contract manufacturers to produce sufficient quantities for large-scale commercialization of our products and product candidates once approved for commercial use. If we do enter into commercial manufacturing arrangements with third parties, these third-party manufacturers will be subject to

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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 drugs 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. Our compounds, once approved for commercial use, will compete with numerous therapeutic treatments offered by these competitors. While we believe that our compounds 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 compounds or technologies obsolete or noncompetitive.

We believe the primary competitors for tasimelteon and Fanapt® are as follows:

For tasimelteon in the treatment of CRSDs, there are no approved direct competitors. Insomnia treatments include, Rozerem® (ramelteon) by Takeda Pharmaceuticals Company Limited, hypnotics such as Ambien® (zolpidem) by sanofi-aventis (including Ambien CR®), Lunesta® (eszopiclone) by Dainippon Sumitomo Pharma, Sonata® (zaleplon) by Pfizer Inc., Silenor® (doxepin) by Somaxon Pharmaceuticals, Inc., generic compounds such as zolpidem, trazodone and doxepin, and over-the-counter remedies such as Benadryl® and Tylenol PM®. The class of melatonin agonists includes Rozerem® (ramelteon) by Takeda Pharmaceuticals Company Limited, Valdoxan® (agemelatine) by Servier, Circadin® (long-acting melatonin) by Neurim Pharmaceuticals and the food supplement melatonin.

For Fanapt® in the treatment of schizophrenia, the atypical antipsychotics Risperdal® (risperidone), including the depot formulation Risperdal® Consta®, and Invega® (paliperidone), including the depot formulation Invega® Sustenna , each by Ortho-McNeil-Janssen Pharmaceuticals, Inc., Zyprexa® (olanzapine), including the depot formulation Zyprexa® Relprevv , by Eli Lilly and Company, Seroquel® (quetiapine) by AstraZeneca PLC, Abilify® (aripiprazole) by BMS/Otsuka Pharmaceutical Co., Ltd., Geodon® (ziprasidone) by Pfizer Inc., Saphris® (asenapine) by Schering-Plough, Latuda® (lurasidone) by Dainippon Sumitomo Pharma, and generic clozapine, as well as the typical antipsychotics haloperidol, chlorpromazine, thioridazine, and sulpiride (all of which are generic).

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 compounds less attractive.

Employees

As of December 31, 2012, we had 40 full-time employees. Of these employees, 24 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 2200 Pennsylvania Avenue NW, Suite 300E, Washington D.C. 20037, and our telephone number is (202) 734-3400. Our website address is www.vandapharma.com and the information contained in, or that can be accessed through, our website is not part of this annual report and should not be considered part of this annual report.

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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, D.C. 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 at www.sec.gov that contains reports, proxy and information statements, and other information regarding issuers, including us, that file electronically with the SEC.

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, 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 the FDA does not accept for filing the NDA that we intend to submit for tasimelteon for the treatment of Non-24, regulatory authorities determine that our clinical trial results for tasimelteon for the treatment of Non-24 do not demonstrate adequate safety and efficacy, or the FDA does not approve an applicable PDUFA date, continued development of tasimelteon will be significantly delayed or terminated, our business will be significantly harmed, and the market price of our stock could decline.

We commenced our Phase III program for tasimelteon for the treatment of Non-24-Hour Disorder (Non-24) in the third quarter of 2010. In December 2012, we reported positive top-line results in a randomized, double-blind, multi-center, placebo-controlled Phase III trial (SET study) that enrolled 84 patients. In January 2013, we announced positive results for the second Phase III study of tasimelteon for the treatment of Non-24. In addition, we have two ongoing open-label safety studies for tasimelteon in treatment of Non-24. Based on the results of our completed trials, we intend to submit a New Drug Application (NDA) with the U.S. Food and Drug Administration (FDA) in mid-2013. We will meet with the FDA in the first quarter of 2013 for a pre-NDA meeting on tasimelteon in the treatment of patients with Non-24. Any adverse developments or results or perceived adverse developments or results with respect to our pre-NDA meeting with the FDA, our regulatory submission or the tasimelteon Phase III program will significantly harm our business and could cause the market price of our stock to decline. Examples of such adverse developments include, but are not limited to:

- the FDA determining that additional clinical studies are required with respect to the Phase III program in Non-24;
- safety, efficacy or other concerns arising from clinical or non-clinical studies in this program; or
- the FDA determining that the Phase III program in Non-24 raises safety concerns or does not demonstrate adequate efficacy.

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We and our partners face heavy government regulation. FDA regulatory approval of our compounds is uncertain and we and our partners are also continually at risk of the FDA requiring us or them to discontinue marketing any compounds that have obtained, or in the future may obtain, regulatory approval.

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

The process of obtaining FDA and other required regulatory approvals and clearances can take many years and will require us and, in the case of partnered products, our partners 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 compound, the disease or condition that the compound is in development for, and the requirements applicable to that particular compound. The FDA can delay, limit or deny approval of a compound for many reasons, including that:

- a compound 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 or our partners do;
- the FDA may not approve our or our partners manufacturing processes or facilities;
- a compound may not be approved for all the indications we or our partners request;
- the FDA may change its approval policies or adopt new regulations;
- the FDA may not meet, or may extend, the Prescription Drug User Fee Act (PDUFA) date with respect to a particular NDA; and
- the FDA may not agree with our or our partners regulatory approval strategies or components of the regulatory filings, such as clinical trial designs.

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

Moreover, the marketing, distribution and manufacture of approved products remain subject to extensive ongoing regulatory requirements. Failure to comply with applicable regulatory requirements could result in, among other things:

- 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; and

criminal prosecution.

Any delay or failure to obtain regulatory approvals for our compounds will result in increased costs, could diminish competitive advantages that we may attain and would adversely affect the marketing and sale of our compounds. Other than Fanapt® in the U.S., Israel and Argentina, we have not received regulatory approval to market any of our compounds in any jurisdiction.

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Even following regulatory approval of our compounds, the FDA may impose limitations on the indicated uses for which such compounds may be marketed, subsequently withdraw approval or take other actions against us, our partners or such compounds that are adverse to our business. The FDA generally approves drugs 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 or modified if problems occur after initial marketing.

We and our partners 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 discovery, research and development work. In addition, we cannot predict the extent to which new governmental regulations might significantly impede the discovery, development, production and marketing of our compounds. We or our partners 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 or the inability to comply with such laws or regulations.

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

Pursuant to our amended and restated sublicense agreement with Novartis, we retained the right to develop and commercialize Fanapt® outside the U.S. and Canada. We intend to market our compounds outside the U.S. and Canada with one or more commercial partners. In order to market our compounds in foreign jurisdictions, we or our partners 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. Additionally, the foreign regulatory approval process may include all of the risks associated with obtaining FDA approval. For all of these reasons, we or our partners 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 or our partners may not be able to file for regulatory approvals and may not receive necessary approvals to commercialize our compounds in any market. The failure to obtain these approvals could harm our business materially.

We continue to explore the regulatory path and commercial opportunity for Fanapt® oral formulation outside of the U.S. and Canada. In December 2012, the European Medicines Agency s (EMA) Committee for Medicinal Product for Human Use (CHMP) issued a negative opinion recommending against approval of Fanaptum (oral iloperidone tablets) for the treatment of schizophrenia in adult patients in the European Union. The CHMP was of the opinion that the benefits of Fanaptum did not outweigh its risks and recommended against marketing authorization at this point in time. In January 2013, we formally appealed the EMA s negative opinion and requested a re-examination of the decision by the CHMP. We may not be successful in obtaining a positive decision from CHMP of our appeal.

Even after we or our partners obtain regulatory approvals of a product, acceptance of such compound in the marketplace is uncertain and failure to achieve market acceptance will prevent or delay our ability to generate revenues.

Even after obtaining regulatory approvals for the sale of our compounds, the commercial success of these compounds 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

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and treatments. The degree of market acceptance of any compound 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 such compound, our ability to attract and maintain corporate partners, including pharmaceutical companies, to assist in commercializing our compounds, receipt of regulatory clearance of marketing claims for the uses that we or our partners are developing and the effectiveness of our and our partners marketing and distribution capabilities. If our approved compounds fail to gain market acceptance, we may be unable to earn sufficient revenue to continue our business. If our approved compounds 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 on a sustained basis or achieve significant revenues.

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 products and product candidates with third parties on terms that may not be attractive to us.

Our activities will necessitate significant uses of working capital throughout 2013 and beyond. As of December 31, 2012, our total cash and cash equivalents and marketable securities were $120.4 million. Our long term capital requirements are expected to depend on many factors, including, among others:

- our ability to commercialize tasimelteon globally;
- the amount of royalty and milestone payments received from our commercial partners;
- our ability to commercialize Fanapt® outside the U.S. and Canada;
- costs of developing and maintaining sales, marketing and distribution channels and our ability to sell our products;
- costs involved in establishing manufacturing capabilities for commercial quantities of our products;
- the number of potential formulations, products and product candidates in development;
- progress with pre-clinical studies and clinical trials;
- time and costs involved in obtaining regulatory (including FDA) approval;
- costs involved in preparing, filing, prosecuting, maintaining and enforcing patent, trademark and other intellectual property claims;
- competing technological and market developments;
- market acceptance of our products;

costs for recruiting and retaining employees and consultants;

costs for training physicians; and

legal, accounting, insurance and other professional and business related costs.

We expect to continue to receive royalty payments and hope to receive commercial and development milestone payments relating to Fanapt® in connection with our amended and restated sublicense agreement with Novartis. Based on the current sales performance of Fanapt® in the U.S. and the decision by Novartis to cease development of the long-acting injectable (or depot) formulation of Fanapt®, we expect that some or all of these commercial and development milestones will not be achieved by Novartis. As a result, we may need to raise additional capital to fund our anticipated operating expenses and execute on our business plans. In our capital-raising efforts, we may seek to sell debt securities or additional equity securities or obtain a bank credit facility, or enter into partnerships or other collaboration agreements. The sale of additional equity or debt securities, if convertible, could result in dilution to our stockholders and may also result in a lower price for our common stock. The incurrence of indebtedness would result in increased fixed obligations and could also result in covenants that could restrict our operations. However, we may not be able to raise additional funds on acceptable

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terms, or at all. If we are unable to secure sufficient capital to fund our planned activities, we may not be able to continue operations, or we may have to enter into partnerships or other 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 partnerships or collaborations, if consummated prior to proof-of-efficacy or safety of a given product, could impair our ability to realize value from that product. If additional financing is not available when required or is not available on acceptable terms, we may be unable to fund our operations and planned growth, develop or enhance our technologies or products, take advantage of business opportunities or respond to competitive market pressures, any of which would materially harm our business, financial condition and results of operations.

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 or our partners ability to demonstrate and maintain a competitive advantage with respect to our compounds and our ability to identify and develop additional products or 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 and product candidates;
- undertaking pre-clinical testing and clinical trials;
- obtaining FDA and other regulatory approvals of products and product candidates; and
- manufacturing, marketing and selling products.

These companies may invest heavily and quickly to discover and develop novel products that could make our compounds obsolete. Accordingly, our competitors may succeed in obtaining patent protection, receiving FDA or foreign regulatory approval or commercializing superior products or other competing products before we do. Technological developments or the FDA or foreign regulatory approval of new therapeutic indications for existing products may make our compounds obsolete or may make them more difficult to market successfully, any of which could have a material adverse effect on our business, results of operations and financial condition.

Fanapt® (and our other compounds, if successfully developed and approved for commercial sale) will compete with a number of drugs and therapies currently manufactured and marketed by major pharmaceutical and other biotechnology companies. Our compounds may also compete with new products currently under development by others or with products which may cost less than our compounds. Physicians, patients, third party payors and the medical community may not accept or utilize any of our compounds that may be approved. If Fanapt® and our other compounds (if and when approved) do not achieve significant market acceptance, our business, results of operations and financial condition would be materially adversely affected. We believe the primary competitors for Fanapt® and tasimelteon are as follows:

- For tasimelteon in the treatment of CRSDs, there are no approved direct competitors. Insomnia treatments include, Rozerem® (ramelteon) by Takeda Pharmaceuticals Company Limited, hypnotics such as Ambien® (zolpidem) by sanofi-aventis (including Ambien CR®), Lunesta® (eszopiclone) by Dainippon Sumitomo Pharma, Sonata® (zaleplon) by Pfizer Inc., Silenor® (doxepin) by Somaxon Pharmaceuticals, Inc., generic compounds such as zolpidem, trazodone and doxepin, and over-the-counter remedies such as Benadryl® and Tylenol PM®. The class of melatonin agonists includes Rozerem® (ramelteon) by Takeda Pharmaceuticals Company Limited, Valdoxan® (agemelatine) by Servier, Circadin® (long-acting melatonin) by Neurim Pharmaceuticals and the food supplement melatonin.

- For Fanapt® in the treatment of schizophrenia, the atypical antipsychotics Risperdal® (risperidone), including the depot formulation Risperdal® Consta®, and Invega® (paliperidone), including the depot formulation Invega® Sustenna , each by Ortho-McNeil-Janssen Pharmaceuticals, Inc., Zyprexa® (olanzapine), including the depot formulation Zyprexa® Relprevv , by Eli Lilly and Company, Seroquel® (quetiapine) by AstraZeneca PLC, Abilify® (aripiprazole) by BMS/Otsuka Pharmaceutical Co.,

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Ltd., Geodon® (ziprasidone) by Pfizer Inc., Saphris® (asenapine) by Schering-Plough, Latuda® (lurasidone) by Dainippon Sumitomo Pharma, and generic clozapine, as well as the typical antipsychotics haloperidol, chlorpromazine, thioridazine, and sulpiride (all of which are generic).

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 compounds less attractive.

We have no experience selling, marketing or distributing products, other than providing assistance to Novartis relating to the U.S. commercialization of Fanapt®, which may make commercializing our products and product candidates difficult.

At present, we have no marketing experience, other than providing assistance to Novartis relating to the U.S. commercialization of Fanapt®. Therefore, in order for us to commercialize Fanapt®, outside the U.S. and Canada, or our other compounds, including tasimelteon, 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, in some instances, rely significantly on sales, marketing and distribution arrangements with our collaborative partners and other third parties. For example, we rely completely on Novartis to market, sell and distribute Fanapt® in the U.S. and Canada.

For the commercialization of Fanapt® outside the U.S. and Canada or our other compounds, we may not be able to establish, other than those currently established, sales and distribution partnerships on acceptable terms or at all. In regard to our current foreign partners and any additional distribution arrangements or other agreements we may enter into, our success will be materially 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 and product candidates 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 products;

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; and

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.

The cost of establishing and maintaining a sales, marketing and distribution organization may exceed its cost effectiveness. If we fail to develop sales and marketing capabilities, if sales efforts are not effective or if costs of developing sales and marketing capabilities exceed their cost effectiveness, our business, results of operations and financial condition could be materially adversely affected.

Novartis began selling, marketing and distributing our first approved product, Fanapt®, in the U.S. in the first quarter of 2010 and we will depend heavily on the success of this product in the marketplace.

Our ability to generate revenue for the next few years will depend substantially on the success of Fanapt® and the sales of this product by Novartis in the U.S. and Canada. The ability of Fanapt® to generate revenue at the levels we expect will depend on many factors, including the following:

the extent and effectiveness of the development, sales and marketing and distribution support Fanapt® receives;

the amount of resources and efforts utilized by Novartis in relation to the commercialization of Fanapt®;

the ability of patients to be able to afford Fanapt® or obtain health care coverage that covers Fanapt®;

acceptance of, and ongoing satisfaction, with Fanapt® by the medical community, patients receiving therapy and third party payers;

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a satisfactory efficacy and safety profile as demonstrated in a broad patient population;

the size of the market for Fanapt®;

successfully expanding and sustaining manufacturing capacity to meet demand;

cost and availability of raw materials;

safety concerns in the marketplace for schizophrenia therapies;

regulatory developments relating to the manufacture or continued use of Fanapt®;

decisions as to the timing of product launches, pricing and discounts;

the competitive landscape for approved and developing therapies that will compete with Fanapt®;

Novartis ability to obtain regulatory approval in Canada for Fanapt® and our or our partners ability to obtain regulatory approval for Fanapt® in countries outside the U.S. and Canada;

our ability to successfully develop and commercialize Fanapt®, including a long-acting injectable (or depot) formulation of Fanapt®, outside of the U.S. and Canada; and

the unfavorable outcome or other negative effects of any potential litigation relating to Fanapt®.

We entered into an amended and restated sublicense agreement with Novartis to commercialize Fanapt® in the U.S. and Canada. As such, we are not directly involved in the marketing or sales efforts for Fanapt® in the U.S. and Canada. Our revenues for the forseeable future depend substantially on royalties and milestone payments we may receive from Novartis. Pursuant to the amended and restated sublicense agreement with Novartis, we received an upfront payment of $200.0 million and are eligible for additional payments totaling up to $265.0 million upon Novartis achievement of certain commercial and development milestones for Fanapt® in the U.S. and Canada. Based on the current sales performance of Fanapt® in the U.S. and the decision by Novartis to cease development of the long-acting injectable (or depot) formulation of Fanapt®, we expect that some or all of these commercial and development milestones will not be achieved by Novartis. We also receive royalties, which, as a percentage of net sales, are in the low double-digits, on net sales of Fanapt® in the U.S. and Canada. Such royalties may not be significant and will depend on numerous factors, many of which we cannot control. We cannot control the amount and timing of resources that Novartis may devote to Fanapt®. If Novartis fails to successfully commercialize Fanapt® in the U.S. or fails to develop and commercialize Fanapt® in Canada, if Novartis efforts are not effective, or if Novartis focuses its efforts on other schizophrenia therapies or schizophrenia drug candidates, our business will be negatively affected. If Novartis does not successfully commercialize Fanapt® in the U.S. or Canada, we will receive limited revenues from them. Although we have developed and continue to develop additional products and product candidates for commercial introduction, we expect to be substantially dependent on sales from Fanapt® for the foreseeable future. For reasons outside of our control, including those mentioned above, sales of Fanapt® may not meet our or financial or industry analysts expectations. Any significant negative developments relating to Fanapt®, such as safety or efficacy issues, the introduction or greater acceptance of competing products or adverse regulatory or legislative developments, will have a material adverse effect on our financial condition and results of operations.

If our compounds are determined to be unsafe or ineffective in humans, whether commercially or in clinical trials, our business will be materially harmed.

Despite the FDA s approval of the NDA for Fanapt® in May 2009 and the positive results of our completed trials for Fanapt® and tasimelteon, we are uncertain whether either of these products will ultimately prove to be effective and safe in humans. Frequently, products 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 our compounds, whether in clinical trials or commercially, may reveal that the compound is ineffective, unacceptably toxic, has other undesirable side effects, is difficult to manufacture on a large scale, is uneconomical, infringes on proprietary rights of another party or is otherwise not fit for further use. If our compounds are determined to be unsafe or ineffective in humans, our business will be materially harmed.

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Clinical trials for our compounds are expensive and their outcomes are uncertain. Any failure or delay in completing clinical trials for our compounds could severely harm our business.

Pre-clinical studies and clinical trials required to demonstrate the safety and efficacy of our compounds are time-consuming and expensive and together take several years to complete. Before obtaining regulatory approvals for the commercial sale of any of our compounds, we or our partners must demonstrate through preclinical testing and clinical trials that such compound is safe and effective for use in humans. We have incurred, and we will continue to incur, substantial expense for, and devote a significant amount of time to, preclinical testing and clinical trials.

Historically, the results from preclinical testing and early clinical trials often have not predicted results of later clinical trials. A number of new drugs have shown promising results in clinical trials, but subsequently failed to establish sufficient safety and efficacy data to obtain necessary regulatory approvals. Clinical trials conducted by us, by our partners or by third parties on our or our partners behalf may not demonstrate sufficient safety and efficacy to obtain the requisite regulatory approvals for our compounds. Regulatory authorities may not permit us or our partners to undertake any additional clinical trials for our compounds, may force us to stop any ongoing clinical trials and it may be difficult to design efficacy studies for our compounds in new indications.

Clinical development efforts performed by us or our partners may not be successfully completed. Completion of clinical trials may take several years or more. The length of time can vary substantially with the type, complexity, novelty and intended use of the compounds and the size of the prospective patient population. The commencement and rate of completion of clinical trials for our compounds may be delayed by many factors, including:

- the inability to manufacture or obtain from third parties materials sufficient for use in pre-clinical studies and clinical trials;
- delays in beginning a clinical trial;
- 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 our compounds during clinical trials;