Vanda Pharmaceuticals Inc.
Form 10-K
February 15, 2018
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UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

Form 10-K

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

For the fiscal year ended December 31, 2017

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

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

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes No

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

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

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

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

As of June 30, 2017, the last business day of the registrant s last completed second quarter, the aggregate market value of the Common Stock held by non-affiliates of the registrant was approximately $715.2 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 and 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 1, 2018 was 45,437,938.

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 2018 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, 2017, 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. Words such as, but not limited to, believe, expect, anticipate, estimate, intend, project, target, goal, likely, will, would, and could, or the negative of these terms and similar expressions c identify 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 ability of Vanda Pharmaceuticals Inc. (we, our, the Company or Vanda) to continue to commercialize HETLIOZ® (tasimelteon) for the treatment of Non-24-Hour Sleep-Wake Disorder (Non-24) in the United States (U.S.) and Europe;
- uncertainty as to the ability to increase market awareness of Non-24 and the market acceptance of HETLIOZ®;
- our ability to continue to generate U.S. sales of Fanapt® (iloperidone) for the treatment of schizophrenia;
- our dependence on third-party manufacturers to manufacture HETLIOZ® and Fanapt® in sufficient quantities and quality;
- our level of success in commercializing HETLIOZ® and Fanapt® in new markets;
- our ability to prepare, file, prosecute, defend and enforce any patent claims and other intellectual property rights;
- a loss of rights to develop and commercialize our products under our license agreements;
- the ability to obtain and maintain regulatory approval of our products, and the labeling for any approved products;
- the timing and success of preclinical studies and clinical trials;
- a failure of our products to be demonstrably safe and effective;

the size and growth of the potential markets for our products and the ability to serve those markets;

our expectations regarding trends with respect to our revenues, costs, expenses, liabilities and cash, cash equivalents and marketable securities;

the scope, progress, expansion, and costs of developing and commercializing our products;

our failure to identify or obtain rights to new products;

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

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

the cost and effects of litigation;

our ability to obtain the capital necessary to fund our research and development or commercial activities;

losses incurred from product liability claims made against us; and

use of our existing cash, cash equivalents and marketable securities.

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.

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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 I 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 we file with the Securities and Exchange Commission from time to time, including on Form 10-Q and Form 8-K, which may supplement, modify, supersede or update those risk factors. As a result of these factors, we cannot assure you that the forward-looking statements in this report will prove to be accurate. Furthermore, if our forward-looking statements prove to be inaccurate, the inaccuracy may be material. In light of the significant uncertainties in these forward-looking statements, you should not regard these statements as a representation or warranty by us or any other person that we will achieve our objectives and plans in any specified time frame, or at all.

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ITEM 1. BUSINESS

Overview

Vanda Pharmaceuticals Inc. (we, our, the Company or Vanda) is a global biopharmaceutical company focused on the development and commercialization of innovative therapies to address high unmet medical needs and improve the lives of patients. Vanda commenced its operations in 2003 and our product portfolio includes:

HETLIOZ® (tasimelteon), a product for the treatment of Non-24-Hour Sleep-Wake Disorder (Non-24), was approved by the U.S. Food and Drug Administration (FDA) in January 2014 and launched commercially in the U.S. in April 2014. In July 2015, the European Commission (EC) granted centralized marketing authorization with unified labeling for HETLIOZ® for the treatment of Non-24 in totally blind adults. HETLIOZ® was commercially launched in Germany in August 2016. HETLIOZ® has potential utility in a number of other circadian rhythm disorders and is presently in clinical development for the treatment of Pediatric Non-24, Jet Lag Disorder and Smith-Magenis Syndrome (SMS).

Fanapt® (iloperidone), a product for the treatment of schizophrenia, the oral formulation of which was approved by the FDA in May 2009 and launched commercially in the U.S. by Novartis Pharma AG (Novartis) in January 2010. Novartis transferred all the U.S. and Canadian commercial rights to the Fanapt® franchise to us on December 31, 2014. Additionally, our distribution partners launched Fanapt® in Israel and Mexico in 2014. Fanapt® has potential utility in a number of other disorders. An assessment of new Fanapt® clinical opportunities is ongoing.

Tradipitant (VLY-686), a small molecule neurokinin-1 receptor (NK-1R) antagonist, which is presently in clinical development for the treatment of chronic pruritus in atopic dermatitis and the treatment of gastroparesis.

VTR-297 (formerly Trichostatin A), a small molecule histone deacetylase (HDAC) inhibitor.

VQW-765 (formerly AQW-051), a Phase II alpha-7 nicotinic acetylcholine receptor partial agonist.

Portfolio of Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) activators and inhibitors.

Since we began operations in March 2003, we have devoted substantially all of our resources to the in-licensing, clinical development and commercialization of our products. Our ability to generate meaningful product sales and achieve profitability largely depends on our level of success in commercializing HETLIOZ® in the U.S. and Europe and Fanapt® in the U.S. alone or with others, to complete the development of our products, and to obtain the regulatory approvals for and to manufacture, market and sell our products. 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 entitled *Risk Factors* and Item 7 of Part II entitled *Management s Discussion and Analysis of Financial Condition and Results of Operations* of this annual report on Form 10-K.

Our activities will necessitate significant uses of working capital in 2018 and beyond. We are currently concentrating our efforts on selling HETLIOZ® and Fanapt® in the U.S. and our continued commercialization of HETLIOZ® in Europe. Additionally, we continue to pursue market approval of HETLIOZ® and Fanapt® in other regions. We will continue to work with our distribution partners on the commercialization of Fanapt® outside the U.S. We see opportunities to grow our commercial products through life cycle management strategies that include the addition of new indications and formulations. 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. Our pipeline includes novel programs that could address largely unmet medical needs.

Our founder and Chief Executive Officer, Mihael H. Polymeropoulos, M.D., started Vanda s operations in early 2003 after establishing and leading the Pharmacogenetics Department at Novartis. In acquiring and developing our products, 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 Strategy

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

Maximize the commercial success of HETLIOZ® and Fanapt®;

Enter into strategic partnerships to supplement our capabilities and to extend our commercial reach;

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Pursue the clinical development and regulatory approval of our products;

Apply our pharmacogenetics and pharmacogenomics expertise to differentiate our products; and

Expand our product portfolio through the identification and acquisition of additional products.

Products

We have the following products on the market or under regulatory review:

Product	Indication	Geography	Select Historical Milestones
HETLIOZ® (tasimelteon)	Non-24	United States	FDA approval in January 2014; Commercial launch in April 2014
		Europe	EC approval in July 2015; Commercial launch in Germany in August 2016
Fanapt® (Oral) (iloperidone)	Schizophrenia	United States	FDA approval in May 2009; Commercial launch in January 2010; U.S. and Canada rights sublicensed to Novartis in October 2009 and reacquired by Vanda in December 2014; Long term maintenance supplemental New Drug Application (sNDA) approval in May 2016
Fanaptum® (Oral) (iloperidone)		Mexico	Market approval in October 2013; Commercial launch in the fourth quarter of 2014 by our local distribution partner
		Israel	Market approval August 2012; Commercial launch in the fourth quarter of 2014 by our local distribution partner

We have the following products in clinical development:

Product	Target Indication	Select Historical Milestones
HETLIOZ® (tasimelteon)	Pediatric Non-24	Initiated a liquid formulation pharmacokinetic study in the fourth quarter of 2016
	SMS	Initiated a placebo controlled study in the fourth quarter of 2016

	Jet Lag Disorder	Initiated a placebo controlled transmeridian travel study in the fourth quarter of 2016; Initiated a placebo controlled simulated jet lag study in the fourth quarter of 2017
Fanapt® (Oral) (iloperidone)	Schizophrenia	Long-acting injectable under evaluation
	Other Disorders	Potential indications are under evaluation including bipolar depression, major depressive disorder and post-traumatic stress disorder nightmares
Tradipitant (VLY-686)	Pruritus in patients with Atopic Dermatitis	Completed a placebo controlled clinical study and reported results in the third quarter of 2017
	Gastroparesis	Initiated a placebo controlled study in fourth quarter of 2016
VTR-297	Oncology	In development for hematologic malignancies
VQW-765	CNS Disorders	Potential indications are under strategic evaluation including cognitive impairment

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HETLIOZ®

Commercial opportunity: Non-24

In January 2014, HETLIOZ® was approved in the U.S. for the treatment of Non-24. Non-24 is a serious, rare and chronic circadian rhythm disorder characterized by the inability to entrain (synchronize) the master body clock with the 24-hour day-night cycle. HETLIOZ® is the first FDA approved treatment for Non-24. HETLIOZ® is a melatonin agonist of the human MT1 and MT2 receptors, with greater specificity for MT2. These receptors are thought to be involved in the control of circadian rhythms. HETLIOZ® is believed to reset the master body clock in the suprachiasmatic nucleus, located in the hypothalamus, resulting in the entrainment and alignment of the body s melatonin and cortisol rhythms to the 24-hour day-night cycle. HETLIOZ® was launched commercially in the U.S. in April 2014. In addition, in July 2015, the EC granted centralized marketing authorization with unified labeling for HETLIOZ® for the treatment of Non-24 in totally blind adults and included post-marketing commitments related to a pediatric investigation plan. This authorization is valid in the 28 countries that are members of the European Union (E.U.), as well as European Economic Area members Iceland, Liechtenstein and Norway. HETLIOZ® was launched commercially in Germany in August 2016.

In January 2010, the FDA granted orphan drug designation status for HETLIOZ® in Non-24 in blind individuals. 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 HETLIOZ® as an orphan medicinal product for the same indication.

Non-24 affects a majority of totally blind individuals, or approximately 80,000 people in the U.S. Blind individuals who develop Non-24 lack the light sensitivity necessary to synchronize the master body clock in the brain with the 24-hour day-night cycle. In sighted individuals, decreased exposure or sensitivity to light and social and physical activity cues may contribute to a free-running circadian rhythm. With the high frequency of mental disorders involving social isolation and cases of Non-24 developing after a change in sleep habits, behavioral factors in combination with physiological tendency may precipitate and perpetuate this disorder in sighted individuals. Hospitalized individuals with neurological and psychiatric disorders can become insensitive to social cues, predisposing them to the development of Non-24.

Most people have a master body clock that naturally runs longer than 24-hours and light is the primary environmental cue that resets it to 24 hours each day. Individuals with Non-24 have a master body clock that is not reset, and continually delays, resulting in prolonged periods of misalignment between their circadian rhythms and the 24-hour day-night cycle, including the timing of melatonin and cortisol secretion. As a result of this misalignment, Non-24 is associated with significant disruption of the sleep-wake cycle and impairments in social and occupational functioning, and marked subjective distress. Individuals with Non-24 cycle in-and out-of phase and suffer from disrupted nighttime sleep patterns and/or excessive daytime sleepiness.

While there are no FDA or EC approved treatments for Non-24 other than HETLIOZ®, there are a number of drugs approved and prescribed for patients with sleep disorders. The most commonly prescribed drugs are hypnotics. See *Competition* below for a discussion of commonly prescribed drugs for patients with sleep disorders.

Therapeutic opportunity: Circadian Rhythm Sleep Disorders

Sleep disorders are segmented into three major categories: primary insomnia, secondary insomnia and circadian rhythm sleep disorders (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 delayed sleep phase disorder, shift work sleep disorder and Non-24. We are planning to develop HETLIOZ® for the treatment of pediatric Non-24. We initiated a pediatric liquid formulation pharmacokinetic study in the fourth quarter of 2016.

We initiated an open label interventional study in patients with SMS in the fourth quarter of 2015 and shared the results at the joint congress of World Association of Sleep Medicine and World Sleep federation in October 2017, which showed that parents of children with SMS reported improvement in sleep quality and a decrease in aberrant behaviors during treatment as compared to baseline. We initiated a SMS placebo controlled study in the fourth quarter of 2016. Enrollment in this study is ongoing. SMS is a rare genetic disorder caused by a deletion on chromosome 17. The U.S. National Institute of Health estimates that SMS affects approximately one in 20,000 births in the U.S.

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We initiated an observational study in Jet Lag Disorder in the fourth quarter of 2015. The data from that study was used to support clinical study design for our two placebo controlled studies. We initiated a placebo controlled transmeridian travel study in the fourth quarter of 2016 and a placebo controlled simulated jet lag study in the fourth quarter of 2017.

Fanapt®

Commercial Opportunity: Schizophrenia

Fanapt® is a product 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. In 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 had exclusive commercialization rights to all formulations of Fanapt® in the U.S. and Canada. In January 2010, Novartis launched Fanapt® in the U.S. On December 31, 2014, Novartis transferred all the U.S. and Canadian commercial rights to the Fanapt® franchise to Vanda as part of a settlement agreement. In June 2015, we announced positive results from REPRIEVE, a Phase III long-term maintenance study that was conducted by Novartis. In May 2016, the FDA approved a sNDA for Fanapt® for the maintenance treatment of schizophrenia in adults.

In July 2017, the EMA s Committee for Medicinal Products 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 E.U. The CHMP was of the opinion that the benefits of Fanaptum® did not outweigh its risks and recommended against marketing authorization. The negative opinion was upheld upon appeal in November 2017.

We received market approval for the commercialization of Fanapt® in Israel in August 2012 and in Mexico in October 2013. Our distribution partners launched Fanapt® in Israel and Mexico in 2014. As of December 31, 2017, we no longer have an active distributor relationship in Mexico.

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 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. See *Competition* below for a discussion of commonly prescribed atypical antipsychotics in addition to Fanapt®.

Pursuant to a settlement agreement with Novartis, we reacquired the U.S. and Canadian rights to the long-acting injectable (depot) formulation of Fanapt®. We are evaluating the commercial opportunity around the depot formulation.

Therapeutic opportunity: Other

We are currently in the process of evaluating potential indications, including bipolar depression, major depressive disorder and post-traumatic stress disorder nightmares.

Tradipitant (VLY-686)

Tradipitant is a small molecule 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, post-operative nausea and vomiting, gastroparesis, alcohol dependence, anxiety, depression and chronic pruritus associated with atopic dermatitis.

We commenced a Phase II clinical study of tradipitant in the treatment of chronic pruritus in patients with atopic dermatitis in 2014. Results from this study, which were announced in March 2015, showed no significant difference from placebo on the pre-specified primary endpoint. Vanda believes this proof of concept study was informative, in that through subsequent analyses, it revealed statistically significant and clinically meaningful responses across multiple outcomes evaluated in individuals with higher blood plasma levels of tradipitant at the time of their pruritus assessments. We initiated a placebo controlled pruritus proof of concept study in the second quarter of 2016. Results from this study, which were announced in September 2017, showed significant improvements in itch and disease severity. These results were presented at the 9th World Congress of Itch in October 2017.

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We initiated a placebo controlled Phase II clinical study of tradipitant in the treatment of gastroparesis in the fourth quarter of 2016.

VTR-297

VTR-297 is a small molecule HDAC inhibitor with potential use as a treatment for several oncology indications. The FDA accepted an Investigational New Drug (IND) application for VTR-297 in 2017 and provided authorization to proceed with the treatment of patients with relapsed and/or refractory hematologic malignancies.

VQW-765

VQW-765 is a Phase II alpha-7 nicotinic acetylcholine receptor partial agonist that we licensed from Novartis on December 31, 2014 pursuant to a settlement agreement. We are evaluating potential indications, including cognitive impairment.

License Agreements

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

HETLIOZ®

In February 2004, we entered into a license agreement with Bristol-Myers Squibb (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 HETLIOZ®. As a result of the FDA s approval of the HETLIOZ® New Drug Application (NDA) in January 2014, we made an $8.0 million milestone payment to BMS in the first quarter of 2014 under the license agreement that was capitalized as an intangible asset and is being amortized over the estimated economic useful life of the related product patents which is the remaining life of the U.S. method of use patent for HETLIOZ® in the U.S. We are obligated to make a future milestone payment to BMS of $25.0 million when cumulative worldwide sales of HETLIOZ® reach $250.0 million, which is expected to occur in the first half of 2018. The probable future $25.0 million milestone obligation was capitalized as an intangible asset in the first quarter of 2015 and is being amortized over the estimated economic useful life of the related product patents which is the remaining life of the U.S. method of use patent for HETLIOZ® in the U.S. Additionally, we are obligated to make royalty payments on HETLIOZ® net sales to BMS in any territory where we commercialize HETLIOZ® for a period equal to the greater of 10 years following the first commercial sale in the territory or the expiry of the new chemical entity patent in that territory. During the period prior to the expiry of the new chemical entity patent in a territory, we are obligated to pay a 10% royalty on net sales in that territory. The royalty rate is decreased by half for countries in which no new chemical entity patent existed or for the remainder of the 10 years after the expiry of the new chemical entity patent. We are also obligated under the 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 HETLIOZ® to use our commercially reasonable efforts to develop and commercialize HETLIOZ®.Either party may terminate the HETLIOZ® license agreement under certain circumstances, including a material breach of the agreement by the other. In the event 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®

Pursuant to the terms of a settlement agreement with Novartis, Novartis transferred all U.S. and Canadian rights in the Fanapt® franchise to us on December 31, 2014. We were obligated to make royalty payments to Sanofi S.A. (Sanofi) and Titan Pharmaceuticals Inc. (Titan) at a percentage rate equal to 23% on annual U.S. net sales of Fanapt® up to $200.0 million, and at a percentage rate in the mid-twenties on sales over $200.0 million through November 2016. In February 2016, we amended the agreement with Sanofi and Titan to remove Titan as the entity through which royalty payments from Vanda are directed to Sanofi following the expiration of the new chemical entity patent for Fanapt® in the U.S. on November 15, 2016. Under the amended agreement, we pay directly to Sanofi a fixed royalty of 3% of net sales from November 16, 2016 through December 31, 2019 related to manufacturing know-how. We made a $2.0 million pre-payment during the year ended December 31, 2016 that applied to this 3% manufacturing know-how royalty. No further royalties on manufacturing know-how are payable by us after December 31, 2019. This amended agreement did not alter Titan s obligation under the license agreement to make royalty payments to Sanofi prior to November 16, 2016 or our obligation to pay Sanofi a fixed royalty on Fanapt® net sales equal up to 6% on Sanofi know-how not

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related to manufacturing under certain conditions for a period of up to 10 years in markets where the new chemical entity patent has expired or was not issued. We may lose our rights to develop and commercialize Fanapt® if we fail to comply with certain requirements in the Titan license agreement regarding our financial condition, or if we fail to comply with certain diligence obligations regarding our development or commercialization activities.

Tradipitant (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, tradipitant, for all human indications. The patent describing tradipitant as a new chemical entity expires in April 2023, except in the U.S., where it expires in June 2024 absent any applicable patent term adjustments. Lilly is eligible to receive future 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. The $4.0 million of pre-NDA approval milestones includes $2.0 million due upon enrollment of the first subject into a Phase III study for tradipitant and $2.0 million due upon the filing of the first marketing authorization for tradipitant in either the U.S. or the E.U. The likelihood of achieving the enrollment of the first subject into a Phase III study for tradipitant was determined to be probable during the third quarter of 2017. As a result, the future obligation of $2.0 million tied to such milestone was recorded as research and development expense in 2017. We are obligated to use commercially reasonable efforts to develop and commercialize tradipitant. 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 tradipitant.

VQW-765

In connection with the settlement agreement with Novartis relating to Fanapt®, we received an exclusive worldwide license under certain patents and patent applications, and other licenses to intellectual property, to develop and commercialize VQW-765, a Phase II alpha-7 nicotinic acetylcholine receptor partial agonist. Pursuant to the license agreement, we are obligated to use commercially reasonable efforts to develop and commercialize VQW-765 and are responsible for all development costs. We have no milestone obligations, but Novartis is eligible to receive tiered-royalties on net sales at percentage rates up to the mid-teens.

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 Novartis 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 Novartis on an exclusive basis, subject to payment by Novartis to us of a royalty on net sales of products that contain VQW-765.

Portfolio of CFTR activators and inhibitors

In March 2017, we entered into a license agreement with the University of California San Francisco (UCSF), under which we acquired an exclusive worldwide license to develop and commercialize a portfolio of CFTR activators and inhibitors. Pursuant to the license agreement, we will develop and commercialize the CFTR activators and inhibitors and are responsible for all development costs under the license agreement, including current pre-investigational new drug development work. The license agreement provides for an initial license fee of $1.0 million, which was paid by

us in the first quarter of 2017, annual maintenance fees and up to $46.0 million in potential regulatory and sales milestone obligations. UCSF is also eligible to receive single-digit tiered royalties on net sales.

Either party may terminate the agreement under certain circumstances. In the event that we terminate the agreement, or if UCSF 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 UCSF. Termination will not relieve Vanda of its obligation to pay royalties or other payments owed, if any, to UCSF under the terms of the agreement.

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 HETLIOZ® in the U.S. and the E.U. and Fanapt® in the U.S., Israel and Mexico, all of our products will require regulatory approval by government agencies prior to commercialization. In particular, human pharmaceutical products are subject to rigorous pre-clinical and clinical trials and other approval procedures of the FDA and similar regulatory authorities in foreign countries. The process of obtaining these approvals and the subsequent compliance with appropriate domestic and foreign laws, rules and regulations require the expenditure of significant time and human and financial resources.

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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.

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 (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.

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

Phase III: refers to expanded controlled and uncontrolled clinical trials. These trials are performed after preliminary evidence suggesting effectiveness of a drug has been obtained. Phase III trials are intended to gather additional information about the effectiveness and safety that is needed to evaluate the overall benefit-risk relationship of the drug and to provide an adequate basis for physician labeling. Phase III trials usually include several hundred to several thousand subjects.

Phase I, II and III testing may not be completed successfully within any specified time period, if at all. The FDA closely monitors the progress of each of the three phases of clinical trials that are conducted in the 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 a 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. 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 followed 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, 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 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 and its acceptance in the medical community.

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

In September 2007, the Food and Drug Administration Amendments Act (FDAAA), was enacted into law, amending the U.S. Federal Food, Drug, and Cosmetic 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 (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 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 (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 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.

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. The U.S. Drug Price Competition and Patent Term Restoration Act of 1984, more commonly known as the Hatch-Waxman Act, 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.

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Foreign regulation

Whether or not we or our partners obtain FDA approval for a product, we must obtain approval by the comparable regulatory authorities of foreign countries before we can commence clinical trials or marketing of the product in those countries. The approval process varies from country to country, and the time may be longer or shorter than that required for FDA approval. The requirements governing the conduct of clinical trials, product licensing, pricing and reimbursement also vary greatly from country to country. Although governed by the applicable country, clinical trials conducted outside of the 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 E.U. regulatory systems, we may submit Marketing Authorization Applications (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 E.U. 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.

Patents and proprietary rights; Hatch-Waxman protection

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

HETLIOZ®, Fanapt®, tradipitant and VQW-765 are covered by new chemical entity and other patents and patent applications. In addition, new chemical entity patent protection has been requested for VTR-297 and CFTR and patent applications for the active ingredients in these products remain pending. For more on these license and sublicense arrangements, see *License Agreements* above. In addition, we have filed for patents based on our own discoveries that seek to provide additional protection for HETLIOZ® and Fanapt®. The primary new chemical entity patent covering Fanapt® expired in November 2016.

The table below is a summary of Orange Book listed patents for our commercial products. Members of these patent families are also issued or pending in a number of major market territories, such as Europe and Japan.

	Number	Type
HETLIOZ®	US 5,856,529	New chemical entity
	US 9,060,995	Method of treatment
	US 9,539,234	Method of treatment
	US 9,549,913	Method of treatment
	US 9,730,910	Method of treatment

	US 9,855,241	Method of treatment
	US RE46604	Method of treatment
Fanapt®	US 8,586,610	Method of treatment
	US 8,652,776	Method of treatment
	US 8,999,638	Method of treatment
	US 9,072,742	Method of treatment
	US 9,074,254	Method of treatment
	US 9,074,255	Method of treatment
	US 9,074,256	Method of treatment
	US 9,138,432	Method of treatment
	US 9,157,121	Method of treatment

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HETLIOZ®

Our rights to the new chemical entity patent covering HETLIOZ® and related intellectual property have been acquired through a license with BMS. HETLIOZ® and its formulations, genetic markers and uses are covered by a total of 14 patent and patent application families worldwide. The primary new chemical entity patent covering HETLIOZ® expires in December 2018 in the U.S. and expired in 2017 in most other markets. The Hatch-Waxman Act provides for an extension of new chemical entity patents for a period of up to five years following the normal expiration of the patent covering that compound to compensate for time spent in development. We believe that HETLIOZ® 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. An application for the five year patent term extension has been filed and is being processed by the U.S. Patent and Trademark Office. The U.S. Patent and Trademark Office has issued six method of use patents for HETLIOZ® that will expire during 2033 and 2034. Both the new chemical entity patent and the method of use patents are listed in the Orange Book.

In Europe, the law provides for ten years of data exclusivity (with the potential for an additional year if the drug is developed for a significant new indication). As such, in Europe, data exclusivity will protect HETLIOZ® for at least ten years from approval. A completed Pediatric Investigation Plan could further extend this exclusivity for two years in an orphan indication, for a total of 12 years of exclusivity. It is also possible that the term of the new chemical entity patent in Europe could be extended by issuance of a supplementary protection certificate (SPC). The European Patent Office has granted our patent application directed to the 20 mg/day dose. This patent will expire normally in 2027. Patent applications directed to the treatment of Non-24, if granted, would provide exclusivity in Europe for this indication until at least 2033.

Outside the U.S. and Europe, data exclusivity will protect HETLIOZ® from generic competition for varying numbers of years depending on the country.

Additional patent applications directed to specific sleep disorders and to methods of treating patients with HETLIOZ®, if issued, would provide exclusivity for such indications and methods of treatment, potentially extending the effective patent protection period in the U.S., Europe, and other major markets.

Fanapt®

The new chemical entity patent for Fanapt®, which expired in 2016, is owned by Sanofi, and other patents and patent applications relating to Fanapt® previously owned by Novartis are now owned by Vanda. We originally obtained exclusive worldwide rights to develop and commercialize the products covered by these patents through license and sublicense arrangements. Then, pursuant to an amended sublicense agreement with Novartis, Novartis retained exclusive commercialization rights to all formulations of Fanapt® in the U.S. and Canada. However, as of December 2014, pursuant to an asset transfer agreement, we acquired all rights in Fanapt®, including in the U.S. and Canada.

Fanapt® and its metabolites, formulations, genetic markers and uses are covered by a total of 17 patent and patent application families in the U.S., Europe, and other markets. The primary new chemical entity patent covering Fanapt® expired in November 2016 in the U.S. and expired in 2010 in major markets outside the U.S. In November 2013, a patent directed to a method of treating patients with Fanapt® based on genotype was issued to us by the U.S. Patent and Trademark Office. This patent, which was listed in the Orange Book in January 2015, is set to expire in 2027, potentially further extending the exclusivity protection of Fanapt®. Additional method of treatment patents were issued and listed in the Orange Book with the latest expected expiry in December 2031. See Note 16, *Legal Matters*, to the consolidated financial statements included in Part II of this annual report on Form 10-K for additional information.

In Europe, the law provides 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. Outside the U.S. and Europe, data exclusivity will protect Fanapt® from generic competition for varying numbers of years depending upon the country. Several other patent applications covering metabolites, uses, formulations and genetic markers relating to Fanapt® extend beyond 2020. The patent family for the microsphere depot formulation of Fanapt® expires in 2024 in the U.S. and 2022 in most of the major markets in Europe. The patent family for the aqueous microcrystals depot formulation of Fanapt® expires in 2023 in the U.S. and in most of the major markets in Europe.

Tradipitant

Lilly owns a new chemical entity patent as well as patent applications directed to polymorphic forms of, and methods of making tradipitant. Thus, tradipitant is covered by a total of three patent and patent application families worldwide, which have been licensed to us. The new chemical entity patent covering tradipitant expires in 2023, except in the U.S., where it expires normally in 2024 subject to any extension that may be received under Hatch-Waxman. We have filed additional patent applications based on discoveries made during recent studies with tradipitant.

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VQW-765

Novartis owns a new chemical entity patent as well as patent applications directed to methods of using VQW-765, VQW-765 formulations, and combinations of VQW-765 with other active pharmaceutical ingredients. The new chemical entity patent expires normally in 2023 in the U.S., Europe, and other markets.

VTR-297

VTR-297 is a small molecule HDAC inhibitor with potential use as a treatment for several oncology indications. We have pending patent applications covering the use of VTR-297 and plan on filing additional applications based on discoveries made throughout the development plan of this molecule.

Portfolio of CFTR activators and inhibitors

Our portfolio of CFTR activators and inhibitors may have broad applicability in addressing a number of high unmet medical needs, including chronic dry eye, constipation, polycystic kidney disease, cholestasis and secretory diarrheas. We plan on filing applications based on discoveries made throughout the development plan of these compounds.

Other Patents

Aside from the new chemical entity patents and other in-licensed patents relating to Fanapt®, HETLIOZ®, tradipitant and VQW-765, we have numerous patent and patent application families, most of which have been filed in key markets including the U.S., relating to our products and development compounds. In addition, we have several other patent application families relating to drugs not presently in clinical studies. The claims in these various patents and patent applications are directed to compositions of matter, including claims covering other products, pharmaceutical compositions and methods of use.

Proprietary Know-how

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 are 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.

Third-Party Reimbursement and Pricing Controls

The Patient Protection and Affordable Care Act, as amended by the Health Care and Education Affordability Reconciliation Act of 2010 (together, PPACA), has changed and is expected to further significantly change the way healthcare is financed by both governmental and private insurers. The provisions of PPACA became effective over various periods from 2010 through 2014. We cannot predict the complete impact of PPACA on pharmaceutical companies because many of PPACA s reforms require the promulgation of detailed regulations to implement the statutory provisions, which has not yet occurred. While we cannot predict the complete impact on federal reimbursement policies this law will have in general or specifically on any product we commercialize, PPACA may result in downward pressure on pharmaceutical reimbursement, which could negatively affect market acceptance of

new products. The rebates, discounts, taxes and other costs resulting from PPACA may have a significant effect on our profitability in the future. In addition, potential reductions of the per capita rate of growth in Medicare spending under PPACA, could potentially limit access to certain treatments or mandate price controls for our products. Moreover, although the U.S. Supreme Court has upheld the constitutionality of most of PPACA, some states have indicated that they intend not to implement certain sections of PPACA, and some members of the U.S. Congress are still working to repeal PPACA. We cannot predict whether these challenges will continue or other proposals will be made or adopted, or what impact these efforts may have on us or our partners.

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 products 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 products.

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

Marketing and Sales

HETLIOZ® was approved in the U.S. for the treatment of Non-24 in January 2014 and commercially launched in the U.S. in April 2014. Additionally, HETLIOZ® was approved in the E.U. for the treatment of Non-24 in totally blind adults in July 2015. We commercially launched HETLIOZ® in Germany in August 2016.

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

Fanapt® was approved in the U.S. for the treatment of schizophrenia in May 2009 and commercially launched in the U.S. in January 2010. 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. Pursuant to the terms of a settlement agreement with Novartis, Novartis transferred all U.S. and Canadian rights in the Fanapt® franchise to Vanda on December 31, 2014.

Fanapt® was launched in Israel and Mexico by our distribution partners in 2014. As of December 31, 2017, we no longer have an active distributor relationship in Mexico. We continue to explore the regulatory path and commercial opportunity for Fanapt® oral formulation in other regions.

Manufacturing

We currently utilize a virtual supply manufacturing and distribution chain in which we do not have our own facilities to manufacture commercial or clinical trial supplies of drugs and we do not have our own distribution facilities. Additionally, we do not intend to develop such facilities for any product in the near future. Instead, we contract with third parties for the manufacture, warehousing, order management, billing and collection and distribution of our products and product candidates.

We expect to continue to rely solely on third-party manufacturers to manufacture drug substance and final drug products for both clinical development and commercial sale. However, there are numerous factors that could cause interruptions in the supply of our products, including regulatory reviews, changes in our sources for manufacturing, disputes with a manufacturer, or financial instability of manufacturers, all of which could negatively impact our operation and our financial results.

We have agreements in place with Patheon Pharmaceuticals Inc. and Patheon Inc. (collectively, Patheon), subsidiaries of Thermo Fisher Scientific, for the manufacture of HETLIOZ® and Fanapt®.

In January 2014, we entered into a manufacturing agreement with Patheon for the manufacture of commercial supplies of HETLIOZ® 20 mg capsules at Patheon s Cincinnati, Ohio manufacturing site. Under the HETLIOZ® manufacturing agreement, we are responsible for supplying the active pharmaceutical ingredient for HETLIOZ® to Patheon and have agreed to certain minimum yearly order requirements. Patheon is responsible for manufacturing the HETLIOZ® 20 mg capsules, conducting quality control and stability testing, and packaging the HETLIOZ® capsules. The

HETLIOZ® manufacturing agreement has an initial term of five years and will automatically renew after the initial term for successive terms of one year each, unless either party gives notice of its intention to terminate the agreement at least twelve months prior to the end of the then current term. Either party may terminate the HETLIOZ® manufacturing agreement under certain circumstances upon specified written notice to the other party.

As part of a settlement agreement, we assumed Novartis manufacturing agreement with Patheon for the manufacture of commercial supplies of Fanapt®. In May 2016, we entered into a new manufacturing agreement with Patheon for the manufacture of commercial supplies of Fanapt® 1, 2, 4, 6, 8, 10 and 12 mg tablets at Patheon s Mississauga, Ontario, Canada manufacturing site. Under the Fanapt® manufacturing agreement, we are responsible for sourcing the supply of the active pharmaceutical ingredient (iloperidone), and have agreed to order from Patheon at least 70% of the total yearly requirement of new units of Fanapt® tables for the U.S. and other specified countries each year for the term of the agreement. The Fanapt® manufacturing agreement has an initial term of five years and will automatically renew after the initial term for successive terms of one year each, unless either party gives notice of its intention to terminate the agreement at least twelve months prior to the end of the then current term. Either party may terminate the Fanapt® manufacturing agreement under certain circumstances upon specified written notice to the other party.

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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.

Research and development expenses amounted to $38.5 million, $29.2 million and $29.1 million for the years ended December 31, 2017, 2016 and 2015, respectively.

Major Customers

Our revenues are generated from product sales and are concentrated with specialty pharmacies and wholesalers. There were six major customers that each accounted for more than 10% of total revenues and, as a group, represented 95% of total revenues for the year ended December 31, 2017.

Competition

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

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

For HETLIOZ® in the treatment of Non-24, there are no FDA approved direct competitors. Sedative-Hypnotic treatments for certain sleep related disorders include, Ambien® (zolpidem) by Sanofi (including Ambien CR®), Lunesta® (eszopiclone) by Sunovion Pharmaceuticals Inc., Sonata® (zaleplon) by Pfizer Inc., Rozerem® (ramelteon) by Takeda Pharmaceuticals Company Limited, Silenor® (doxepin) by Pernix Therapeutics, Belsomra® (suvorexant) by Merck & Co., Inc., generic products 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® (agomelatine) by Servier, Circadin® (long-acting melatonin) by Neurim Pharmaceuticals Ltd. and the food supplement melatonin. Shift work and excessive sleepiness disorder treatments include Nuvigil® (armodafinil) and Provigil® (modafinil) both by Teva Pharmaceutical Industries Ltd.

For Fanapt® in the treatment of schizophrenia, the atypical antipsychotics competitors are 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 , each by Eli Lilly and Company, Seroquel® and Seroquel XR® (quetiapine) by AstraZeneca PLC, Abilify® (aripiprazole) by Otsuka America Pharmaceutical Inc., Abilify Maintena® (the depot formulation of Abilify®) by Lundbeck/Otsuka America Pharmaceutical Inc., Geodon® (ziprasidone) by Pfizer Inc., Saphris® (asenapine) by Allergan plc, Latuda® (lurasidone) by Sunovion Pharmaceuticals Inc., Rexulti® (brexpiprazole) by Lundbeck/Otsuka America Pharmaceutical, Inc., Aristada (aripiprazole lauroxil) extended-release injectible suspension by Alkermes, Inc., Vraylar (cariprazine) by Teva Pharmaceutical Industries Ltd., 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 products before others are able to develop competitive products. Our ability to compete successfully will also depend on our ability to attract and retain skilled and experienced personnel. Additionally, our ability to compete may be affected because insurers and other third-party payors in some cases seek to encourage the use of cheaper, generic products, which could make our products less attractive.

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Employees

We had 273 full-time employees as of December 31, 2017, compared with 142 employees as of December 31, 2016. 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.

Available Information

We file annual, quarterly, and current reports, proxy statements, and other documents with the Securities and Exchange Commission (SEC) under the Securities Exchange Act of 1934 (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 a 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

Our business, financial condition and operating results can be affected by a number of factors, whether currently known or unknown, including but not limited to those described below, any one or more of which could, directly or indirectly, cause our actual operating results and financial condition to vary materially from past, or anticipated future, operating results and financial condition. Any of these factors, in whole or in part, could materially and adversely affect our business, financial condition, operating results and the price of our common stock.

The following discussion of risk factors contains forward-looking statements. These risk factors may be important to understanding any statement in this annual report on Form 10-K or elsewhere. The following information should be read in conjunction with the consolidated financial statements and related notes in Part I, Item 1, Financial Statements and Part I, Item 2, Management s, Discussion and Analysis of Financial Condition and Results of Operations.

Because of the following factors, as well as other factors affecting our financial condition and operating results, past financial performance should not be considered to be a reliable indicator of future performance, and investors should

not use historical trends to anticipate results or trends in future periods.

Risks related to our business and industry

We are dependent on the commercial success of HETLIOZ® and Fanapt®.

Our future success is currently substantially dependent upon the commercial success of HETLIOZ® for the treatment of Non-24-Hour Sleep-Wake Disorder (Non-24) and Fanapt® for the treatment of schizophrenia.

In January 2014, the U.S. Food and Drug Administration (FDA) approved our New Drug Application (NDA) for HETLIOZ® for the treatment of Non-24 and in April 2014, we commenced the U.S. commercial launch of HETLIOZ®. In July 2015, the European Commission (EC) granted centralized marketing authorization with unified labeling for HETLIOZ® for the treatment of Non-24 in totally blind adults, and in August 2016 we commenced the commercial launch of HETLIOZ® in Germany. This authorization is valid in the 28 countries that are members of the European Union (E.U.), as well as European Economic Area members Iceland, Liechtenstein and Norway.

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In the first quarter of 2015, we acquired the U.S. commercial rights to Fanapt®, and began selling, marketing and distributing Fanapt® in the U.S.

Our ability to generate significant product revenue from sales of HETLIOZ® and Fanapt®, both in the U.S. and abroad, in the near term will depend on, among other things, our ability to:

- defend our patents and intellectual property from generic competition;
- maintain commercial manufacturing arrangements with third-party manufacturers;
- produce, through a validated process, sufficiently large quantities of inventory of our products to meet demand;
- continue to maintain and grow a wide variety of internal sales, distribution and marketing capabilities sufficient to sustain growth in sales of our products;
- gain broad acceptance of our products from physicians, health care payors, patients, pharmacists and the medical community;
- properly price and obtain adequate coverage and reimbursement of these products by governmental authorities, private health insurers, managed care organizations and other third-party payors;
- maintain compliance with ongoing labeling, packaging, storage, advertising, promotion, recordkeeping, safety and other post-market requirements;
- obtain regulatory approval to expand the labeling of our approved products for additional indications;
- obtain regulatory approval for HETLIOZ® or Fanapt® in additional countries;
- adequately protect against and effectively respond to any claims by holders of patents and other intellectual property rights that our products infringe their rights; and
- adequately protect against and effectively respond to any unanticipated adverse effects or unfavorable publicity that develops in respect to our products, as well as the emergence of new or existing competitive products, which may be proven to be more clinically effective and cost-effective.

We expect to continue to incur significant expenses and to utilize a substantial portion of our cash resources as we continue the commercialization of HETLIOZ® and Fanapt®, evaluate foreign market opportunities for HETLIOZ® and Fanapt® and continue to grow our operational capabilities, both domestically and abroad. This activity represents a significant investment in the commercial success of HETLIOZ® and Fanapt®, which is uncertain.

If our continued commercial efforts are not successful with respect to HETLIOZ® and Fanapt® in the U.S., Europe or other jurisdictions in which these products may be approved for sale, our ability to generate increased product sales revenue may be jeopardized and, consequently, our business may be seriously harmed.

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

Growth of HETLIOZ® and Fanapt® may be slow or limited for a variety of reasons including competing products or unanticipated safety issues. If either HETLIOZ® or Fanapt® is not successful in gaining broad commercial acceptance, our business would be harmed.

Any increase in sales of HETLIOZ® and Fanapt® will be dependent on several factors, including our ability to educate physicians and to increase physician awareness of the benefits and cost-effectiveness of our products relative to competing products. The degree of further market acceptance of any of our products or market acceptance of approved product candidates among physicians, patients, health care payors and the medical community will depend on a number of factors, including but not limited to:

acceptable evidence of safety and efficacy;

relative convenience and ease of administration;

the prevalence and severity of any adverse side effects;

availability of alternative treatments; and

pricing and cost effectiveness.

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In addition, HETLIOZ® and Fanapt® are subject to continual review by the FDA, and we cannot assure that newly discovered or reported safety issues will not arise. With the use of any newly marketed drug by a wider patient population, serious adverse events may occur from time to time that initially do not appear to relate to the drug itself. Any safety issues could cause us to suspend or cease marketing of our approved products, cause us to modify how we market our approved products, subject us to substantial liabilities and adversely affect our revenues and financial condition. In the event of a withdrawal of either HETLIOZ® or Fanapt® from the market, our revenues would decline significantly and our business would be seriously harmed.

We may enter into third party collaborations from time to time in order to commercialize our products. If we are unable to identify or enter into an agreement with any material third-party collaborator, if our collaborations with any such third-party are not commercially successful or if our agreement with any such third-party is terminated or allowed to expire, we could be adversely affected financially or our business reputation could be harmed.

Our business strategy includes entering into collaborations with corporate collaborators for the commercialization of HETLIOZ®, Fanapt® and our other products. Areas in which we may potentially enter into third-party collaboration arrangements include joint sales and marketing arrangements for sales and marketing in certain E.U. countries and elsewhere outside of the U.S., and future product development arrangements. If we are unable to identify or enter into an agreement with any material third-party collaborator, this could result in an adverse effect on our business, results of operations or financial condition. Any arrangements we do enter into may not be scientifically or commercially successful. The termination of any of these arrangements might adversely affect our ability to develop, commercialize and market our products.

The success of our collaboration arrangements will depend heavily on the efforts and activities of our collaborators. Our collaborators will have significant discretion in determining the efforts and resources that they will apply to these collaborations. We expect that the risks which we face in connection with these future collaborations will include the following:

- our collaboration agreements are expected to be for fixed terms and subject to termination under various circumstances, including, in many cases, on short notice without cause;
- our collaborators may develop and commercialize, either alone or with others, products and services that are similar to or competitive with our products which are the subject of their collaboration with us; and
- our collaborators may change the focus of their commercialization efforts.

In recent years there have been a significant number of mergers and consolidations in the pharmaceutical and biotechnology industries, some of which have resulted in the participant companies reevaluating and shifting the focus of their business following the completion of these transactions. The ability of our products to reach their potential could be limited if any of our future collaborators decreases or fails to increase spending relating to such products.

Collaborations with pharmaceutical companies and other third-parties often are terminated or allowed to expire by the other party. With respect to our future collaborations, any such termination or expiration could adversely affect us financially as well as harm our business reputation.

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

Even after obtaining regulatory approvals for the sale of our products, the commercial success of these products will depend, among other things, on their acceptance by physicians, patients, third-party payors and other members of the medical community as therapeutic and cost-effective alternatives to competing products and treatments. The degree of market acceptance of any product 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 product, our ability to attract and maintain corporate partners, including pharmaceutical companies, to assist in commercializing our products, 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 products fail to gain market acceptance or 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.

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We rely and will continue to rely on outsourcing arrangements for many of our activities, including clinical development and supply of HETLIOZ®, Fanapt® and our other products.

As of December 31, 2017, we had 273 full-time employees, including our sales team. We rely on outsourcing arrangements for a significant portion of our activities, including distribution, clinical research and development, data collection and analysis and manufacturing, as well as for certain functions as a public company. We have limited control over these third parties and we cannot guarantee that they will perform their obligations in an effective and timely manner.

Disruptions to our HETLIOZ® or Fanapt® supply chains could materially affect our level of success in commercializing HETLIOZ® or Fanapt®, thereby reducing our future earnings and prospects.

A loss or disruption with any one of our manufacturers or suppliers could disrupt the supply of HETLIOZ® or Fanapt®, possibly for a significant time period, and we may not have sufficient inventories to maintain supply before the manufacturer or supplier could be replaced or the disruption is resolved. In addition, marketed drugs and their contract manufacturing organizations are subject to continual review, including review and approval of their manufacturing facilities and the manufacturing processes, which can result in delays in the regulatory approval process and/or commercialization. Introducing a replacement or backup manufacturer or supplier for HETLIOZ® or Fanapt® requires a lengthy regulatory and commercial process and there can be no guarantee that we could obtain necessary regulatory approvals in a timely fashion or at all. In addition, it is difficult to identify and select qualified suppliers and manufacturers with the necessary technical capabilities, and establishing new supply and manufacturing sources involves a lengthy and technical engineering process.

Failure to comply with government regulations regarding the sale and marketing of our products could harm our business.

Pharmaceutical companies are subject to extensive government regulation and oversight by government authorities in countries in which they do business. As a result, we may become subject to governmental actions which could materially and adversely affect our business, results of operations and financial condition, certain of which are described below.

Pharmaceutical Pricing and Reimbursement

In U.S. markets, our ability and that of our partners to commercialize our products successfully, and to attract commercialization partners for our products, depends in significant part on the availability of adequate financial coverage and reimbursement from third-party payors, including, in the U.S., governmental payors such as the Medicare and Medicaid programs, managed care organizations, and private health insurers.

We participate in the Medicaid Drug Rebate Program for both HETLIOZ® and Fanapt®. Under the Medicaid Drug Rebate Program, we are required to pay a rebate to each state Medicaid program for our covered outpatient drugs that are dispensed to Medicaid beneficiaries and paid for by a state Medicaid program as a condition of having our drugs eligible for coverage under Medicaid and Medicare Part B. Those rebates are based on pricing data that are reported by us on a monthly and quarterly basis to the Centers for Medicare & Medicaid Services (CMS). Federal law requires that any company that participates in the Medicaid Drug Rebate Program also participate in the Public Health Service s 340B drug pricing discount program (340B program), in order for the manufacturer s drugs to be eligible for coverage under Medicaid and Medicare Part B. The 340B program requires participating manufacturers to agree to charge statutorily-defined covered entities no more than the 340B ceiling price for the manufacturer s covered outpatient drugs. The ceiling price can represent a significant discount and is based on the pricing data reporting to the Medicaid

Drug Rebate Program.

The Patient Protection and Affordable Care Act, as amended by the Health Care and Education Affordability Reconciliation Act of 2010 (together, PPACA) expanded the 340B program to include additional entity types: certain free-standing cancer hospitals, critical access hospitals, rural referral centers and sole community hospitals, each as defined by PPACA. PPACA exempts drugs designated under section 526 of the FDC Act as orphan drugs from the ceiling price requirements for these newly-eligible entities.

PPACA also obligates the Health Resources and Services Administration (HRSA) to create regulations and processes to improve the integrity of the 340B program and to update the agreement that manufacturers must sign to participate in the 340B program. HRSA issued a final regulation in January of 2017 regarding the calculation of the 340B ceiling price and the imposition of civil monetary penalties on manufacturers that knowingly and intentionally overcharge covered entities, although that regulation has been withdrawn and is not currently applicable. The withdrawn final regulation regarding the 340B program included a requirement that a manufacturer calculate the 340B ceiling price on a quarterly basis, the requirement that a manufacturer charge $0.01 per unit of measure if the 340B ceiling price calculation results in a ceiling price that equals zero (penny pricing), the methodology manufacturers must use when estimating the ceiling price for a new covered outpatient drug, an explanation of how a civil monetary penalty (CMP) would be imposed on a manufacturer that knowingly and intentionally overcharges a covered entity; and an explanation of what would constitute an instance of overcharging to trigger a CMP. HRSA recently issued a proposed regulation regarding an administrative

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dispute resolution process for the 340B program. Any final regulations and guidance could affect our obligations under the 340B program in ways we cannot anticipate. In addition, legislation may be introduced that, if passed, would further expand the 340B program to additional covered entities or otherwise expand the 340B program.

Federal law also requires that for a drug manufacturer s products to be eligible for coverage under the Medicaid and Medicare Part B programs and to be purchased by certain federal agencies and grantees, the manufacturer must participate in the Department of Veterans Affairs Federal Supply Schedule (FSS), pricing program, established by Section 603 of the Veterans Health Care Act of 1992. Manufacturers that participate in the FSS pricing program must list their covered (innovator and authorized generic) drugs on an FSS contract and charge no more than Federal Ceiling Price (FCP), to the Department of Veterans Affairs, Department of Defense, Public Health Service, and Coast Guard when those agencies purchase from the FSS contract or a depot contract. FCP is calculated based on non-federal average manufacturer price data, which manufacturers must submit quarterly and annually. In addition, because our products are available in the retail and specialty pharmacy setting, we are required to provide rebates to the Department of Defense for prescriptions dispensed to Tricare beneficiaries from Tricare retail network pharmacies under the Tricare Retail Refund Program. To the extent we choose to participate in these government healthcare programs for our current and future products, these and other requirements may affect our ability to profitably sell any product for which we obtain marketing approval.

Pricing and rebate calculations vary among products and programs. The calculations are complex and will often be subject to interpretation by us, governmental or regulatory agencies and the courts. If we become aware that our reporting of pricing data for a prior quarter was incorrect, we will be obligated to resubmit the corrected data. For the Medicaid Drug Rebate Program, corrected data must be submitted for a period not to exceed 12 quarters from the quarter in which the data originally were due. Such restatements and recalculations increase our costs for complying with the laws and regulations governing the Medicaid Drug Rebate Program and other governmental pricing programs.

We may be liable for errors associated with our submission of pricing data. If we are found to have knowingly submitted false pricing data to the Medicaid program or the FSS pricing program, we may be liable for civil monetary penalties in the amount of up to $100,000 per item of false information. Our failure to submit pricing data to the Medicaid program or the FSS pricing program on a timely basis could result in a civil monetary penalty of $10,000 per day for each day the information is late. Such failure also could be grounds for CMS to terminate our Medicaid drug rebate agreement, which is the agreement under which we would participate in the Medicaid Drug Rebate Program. In the event that CMS terminates our rebate agreement, our products may no longer be eligible for coverage under Medicaid or Medicare Part B. There can be no assurance that our submissions will not be found to be incomplete or incorrect.

Third-party payors decide which drugs they will cover and establish reimbursement and co-pay levels. Third-party payors are increasingly challenging the prices charged for medical products and services and examining their cost effectiveness, in addition to their safety and efficacy. We may need to conduct expensive pharmacoeconomic studies in order to demonstrate the cost effectiveness of our products. Even with such studies, any of our products that are commercialized may be considered less cost-effective than other products, and third-party payors may not provide coverage and reimbursement, in whole or in part, for our products.

Political, economic and regulatory influences are subjecting the healthcare industry in the U.S. to fundamental changes. There have been, and we expect there will continue to be, legislative and regulatory proposals to change the healthcare system and reimbursement systems in ways that could impact our ability and that of our partners to profitably sell commercialized products.

Payors also are increasingly considering new metrics as the basis for reimbursement rates. It is difficult to project the impact of these evolving reimbursement mechanics on the willingness of payors to cover any of our commercialized products.

In addition, we anticipate that a significant portion of our or our partners revenue from sales of commercialized products will be obtained through government payors, including Medicare and Medicaid. Any failure to obtain eligibility for coverage under those programs for products we are able to commercialize would have a material adverse effect on revenues and royalties from sales of such products.

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Interactions with Healthcare Providers

Physicians and other healthcare providers often play a primary role in the recommendation and prescription of pharmaceutical products. Manufacturers of branded prescription drugs are subject to broadly applicable fraud and abuse and other healthcare laws and regulations that may constrain the business or financial arrangements and relationships through which manufacturers market, sell and distribute the products for which they obtain marketing approval. Some of the laws and regulations that may affect our ability to operate are described below.

Anti-Kickback Laws

The federal Anti-Kickback Statute prohibits, among other things, knowingly and willfully offering, paying, soliciting, or receiving remuneration, directly or indirectly, in cash or in kind, to induce or reward the purchasing, leasing, ordering or arranging for the purchase, lease, or order of any health care item or service reimbursable under federal healthcare programs such as Medicare and Medicaid. The term remuneration has been broadly interpreted to include anything of value, and the government can establish a violation of the Anti-Kickback Statute without proving that a person or entity had actual knowledge of the law or specific intent to violate it. This statute has been interpreted to apply to arrangements between pharmaceutical manufacturers on the one hand and prescribers, purchasers, patients, and formulary managers on the other. There are a number of statutory exceptions and regulatory safe harbors protecting certain common activities from prosecution or other regulatory sanctions, however, the exceptions and safe harbors are drawn narrowly. Failure to meet all of the requirements of a particular statutory exception or regulatory safe harbor does not make the conduct per se illegal under the Anti-Kickback Statute, but the legality of the arrangement will be evaluated on a case-by-case basis based on the totality of the facts and circumstances. A number of states also have anti-kickback laws that establish similar prohibitions that may apply to items or services reimbursed by government programs, as well as any third-party payors, including commercial payors. Violations of the Anti-Kickback Statute are punishable by imprisonment, criminal fines, civil monetary penalties and exclusion from the participation in federal healthcare programs, such as Medicare and Medicaid.

Prescription Drug Marketing Act

As part of the sales and marketing process, pharmaceutical companies frequently provide healthcare providers with samples of approved drugs. The Prescription Drug Marketing Act (PDMA) imposes requirements and limitations upon the distribution of drugs and drug samples, and prohibits states from licensing distributors of prescription drugs unless the state licensing program meets certain federal guidelines that include minimum standards for storage and handling, as well as record keeping and other requirements. Violations of the PDMA may result in criminal and civil penalties. In addition, the PPACA imposes annual reporting requirements related to sample distribution.

False Claims Act

The federal civil False Claims Act prohibits, among other things, knowingly presenting, or causing to be presented false or fraudulent claims for payment of government funds and knowingly making, or causing to be made or used, a false record or statement to get a false claim paid. Certain marketing practices may implicate the federal civil False Claims Act, including promotion of pharmaceutical products for unapproved uses, providing free product to customers with the expectation that the customer would bill federal programs for the product, or inflating prices reported to private price publication services used to set drug reimbursement rates under federal healthcare programs. In addition, PPACA amended the Social Security Act to provide that a claim including items or services resulting from a violation of the Anti-Kickback Statute constitutes a false claim for purposes of the False Claims Act. Actions under the False Claims Act may be brought by the government or as a qui tam action by a private individual in the name of the government. False Claims Act liability is potentially significant in the healthcare industry because the

statute provides for treble damages and mandatory penalties of $5,500 to $11,000 per false claim or statement, which increased to a range of $10,957 to $21,916 in February 2017. Violations of the False Claims Act are also punishable by exclusion from participation in federal healthcare programs, such as Medicare and Medicaid. Pharmaceutical and other life sciences companies often resolve allegations without admissions of liability for significant and sometimes material amounts to avoid the uncertainty of treble damages and per claim penalties that may awarded in litigation proceedings. They may be required, however, to enter into corporate integrity agreements with the government, which may impose substantial costs on companies to ensure compliance.

Health Insurance Portability and Accountability Act

The federal Health Insurance Portability and Accountability Act of 1996 (HIPAA), includes federal criminal statutory provisions that prohibit among other actions, knowingly and willfully executing, or attempting to execute, a scheme to defraud any healthcare benefit program, including private third-party payors, knowingly and willfully embezzling or stealing from a healthcare benefit program, willfully obstructing a criminal investigation of a healthcare offense, and knowingly and willfully falsifying, concealing or covering up a material fact or making any materially false, fictitious or fraudulent statement in connection with the delivery of or payment for healthcare benefits, items or services.

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HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act (HITECH) and their implementing regulations, impose certain requirements and restrictions on certain types of individuals and entities relating to the privacy and security of individually identifiable health information. Among other things, HITECH makes HIPAA s security standards directly applicable not only to covered entities (e.g. health care providers and health plans), but also to business associates, i.e., independent contractors or agents of covered entities that receive or obtain protected health information in connection with providing a service for or on behalf of a covered entity. HITECH also created four new tiers of civil monetary penalties, amended HIPAA to make civil and criminal penalties directly applicable to business associates, and gave state attorneys general new authority to file civil actions for damages or injunctions in federal courts to enforce the federal HIPAA laws and seek attorneys fees and costs associated with pursuing federal civil actions.

Physician Payment Sunshine Act

The federal Physician Payment Sunshine Act requires manufacturers of drugs, devices, biologics and medical supplies for which payment is available under Medicare, Medicaid or the Children s Health Insurance Program to report annually (with certain exceptions) to CMS, information related to payments or other transfers of value made to physicians and teaching hospitals, and requires applicable manufacturers and group purchasing organizations to report annually to CMS ownership and investment interests held by physicians and their immediate family members and payments or other transfers of value to such physician owners. Failure to report relevant data may result in civil fines and/or penalties.

Foreign Corrupt Practices Act

The U.S. Foreign Corrupt Practices Act (FCPA), prohibits U.S. corporations and their representatives and intermediaries from offering, promising, authorizing or making payments to any foreign government official, government staff member, political party or political candidate in an attempt to obtain or retain business abroad. The scope of the FCPA includes interactions with certain healthcare professionals in many countries. Other countries have enacted similar anti-corruption laws and/or regulations.

Analogous State and Foreign Laws

Many states also have statutes or regulations similar to the federal laws described above, including state anti-kickback and false claims laws. In addition to requiring reporting transfers of value, some states have imposed price reporting requirements, and an increasing number of countries worldwide have either adopted or are considering similar laws requiring disclosure of various interactions with healthcare professionals. These state laws apply to items and services reimbursed under Medicaid and other state programs, or, in several states, apply regardless of the payor. In addition, a number of states require pharmaceutical companies to report expenses relating to the marketing and promotion of pharmaceutical products and to report gifts and payments to individual physicians in the states. Other states restrict when pharmaceutical companies may provide meals to prescribers or engage in other marketing related activities, or require pharmaceutical companies to implement compliance programs or marketing codes of conduct. Compliance with these laws requires significant resources and companies that do not comply may face civil penalties or other consequences.

Outside the U.S., we are subject to similar regulations in those countries where we market and sell products, including with respect to transparency, bribery and other laws mentioned above. In some foreign countries, including major markets in the E.U. and Japan, the pricing of prescription pharmaceuticals is subject to governmental control. In these countries, pricing negotiations with governmental authorities can take nine to twelve months or longer after the receipt of regulatory marketing approval for a product. To obtain reimbursement or pricing approval in some countries, we

may be required to conduct a clinical trial that compares the cost-effectiveness of our product to other available therapies. Our business could be materially harmed if reimbursement of our products is unavailable or limited in scope or amount or if pricing is set at unsatisfactory levels.

Additionally, drug prices are under significant scrutiny, and along with other health care costs, continue to be subject to intense political and societal pressures, which we anticipate will continue and escalate, including on a global basis. As a result, our business and reputation may be harmed, our stock price may be adversely impacted and experience periods of volatility, and our results of operations may be adversely impacted.

Other Laws and Regulations

There are evolving legal requirements and other statutory and regulatory regimes that will continue to affect our business.

Efforts to ensure that business activities and business arrangements comply with applicable healthcare laws and regulations can be costly for manufacturers of branded prescription products. If a manufacturer s operations, including activities conducted by its sales or marketing teams, are found to be in violation of any of these laws or any other governmental regulations that apply to the company, the company may be subject to significant civil, criminal and administrative sanctions, including imprisonment, monetary penalties, damages, fines, exclusion from participation in federal healthcare programs, such as Medicare and Medicaid, and the curtailment or restructuring of operations.

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

We intend to market our products, alone or with others, in foreign jurisdictions. In order to market our products 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 products in any market. The failure to obtain these approvals could harm our business materially.

We rely on a limited number of specialty pharmacies for distribution of HETLIOZ® in the U.S., and the loss of one or more of these specialty pharmacies or their failure to distribute HETLIOZ® effectively would materially harm our business.

HETLIOZ® is only available for distribution through a limited number of specialty pharmacies in the U.S. A specialty pharmacy is a pharmacy that specializes in the dispensing of medications for complex or chronic conditions, which often require a high level of patient education and ongoing management. The use of specialty pharmacies involves certain risks, including, but not limited to, risks that these specialty pharmacies will:

- not provide us accurate or timely information regarding their inventories, the number of patients who are using HETLIOZ® or complaints about HETLIOZ®;
- reduce their efforts or discontinue to sell or support or otherwise not effectively sell or support HETLIOZ®;
- not devote the resources necessary to sell HETLIOZ® in the volumes and within the time frames that we expect;
- be unable to satisfy financial obligations to us or others; or
- cease operations.

In addition, if one or more of our specialty pharmacies do not fulfill their contractual obligations to us, or refuse or fail to adequately serve patients, or their agreements are terminated without adequate notice, shipments of HETLIOZ®, and associated revenues, would be adversely affected. We expect that it would take a significant amount of time if we were required to replace one or more of our specialty pharmacies.

Our revenues from Fanapt® are substantially dependent on sales through a limited number of wholesalers, and such revenues may fluctuate from quarter to quarter.

We sell Fanapt® primarily through a limited number of pharmaceutical wholesalers in the U.S. The use of pharmaceutical wholesalers involves certain risks, including, but not limited to, risks that these pharmaceutical wholesalers will:

- not provide us accurate or timely information regarding their inventories, demand from wholesaler customers buying Fanapt® or complaints about Fanapt®;
- reduce their efforts or discontinue to sell or support or otherwise not effectively sell or support Fanapt®;
- not devote the resources necessary to sell Fanapt® in the volumes and within the time frames that we expect;
- be unable to satisfy financial obligations to us or others; or
- cease operations.

Additionally, our reliance on a small number of wholesalers could cause revenues to fluctuate from quarter to quarter based on the buying patterns of these wholesalers. In addition, if any of these wholesalers fails to pay on a timely basis or at all, our business, financial condition and results of operations could be materially adversely affected.

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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 products and our ability to identify and develop additional products. Large, fully integrated pharmaceutical companies, either alone or together with collaborative partners, have substantially greater financial resources and have significantly greater experience than we do in:

developing products;

undertaking pre-clinical testing and clinical trials;

obtaining FDA and other regulatory approvals of products; and

manufacturing, marketing and selling products.

These companies may invest heavily and quickly to discover and develop novel products that could make our products 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 products 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.

Our products, 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 products may also compete with new products currently under development by others or with products which may cost less than our products. Physicians, patients, third party payors and the medical community may not accept or utilize any of our products that may be approved. If HETLIOZ®, Fanapt® and our other products, 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 HETLIOZ® and Fanapt® are as follows:

For HETLIOZ® in the treatment of Non-24, there are no FDA approved direct competitors. Sedative-Hypnotic treatments for certain sleep related disorders include, Ambien® (zolpidem) by Sanofi (including Ambien CR®), Lunesta® (eszopiclone) by Sunovion Pharmaceuticals Inc., Sonata® (zaleplon) by Pfizer Inc., Rozerem® (ramelteon) by Takeda Pharmaceuticals Company Limited, Silenor® (doxepin) by Pernix Therapeutics, Belsomra® (suvorexant) by Merck & Co., Inc., generic products 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® (agomelatine) by Servier, Circadin® (long-acting melatonin) by Neurim Pharmaceuticals Ltd. and the food supplement melatonin. Shift work and excessive sleepiness disorder treatments include Nuvigil® (armodafinil) and Provigil® (modafinil) both by Teva Pharmaceutical Industries Ltd.

For Fanapt® in the treatment of schizophrenia, the atypical antipsychotics competitors are 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 , each by Eli Lilly and Company, Seroquel® and Seroquel XR® (quetiapine) by AstraZeneca PLC, Abilify® (aripiprazole) by Otsuka America Pharmaceutical Inc., Abilify Maintena® (the depot formulation of Abilify®) by Lundbeck/Otsuka America Pharmaceutical Inc., Geodon® (ziprasidone) by Pfizer Inc., Saphris® (asenapine) by Allergan plc, Latuda® (lurasidone) by Sunovion Pharmaceuticals Inc., Rexulti® (brexpiprazole) by Lundbeck/Otsuka America Pharmaceutical, Inc., Aristada (aripiprazole lauroxil) extended-release injectible suspension by Alkermes, Inc., Vraylar (cariprazine) by Teva Pharmaceutical Industries Ltd., and generic clozapine, as well as the typical antipsychotics haloperidol, chlorpromazine, thioridazine, and sulpiride (all of which are generic). Additionally, we may face competition from newly developed generic products. Under the Hatch-Waxman Act newly approved drugs and indications may benefit from a statutory period of non-patent marketing exclusivity. The Hatch-Waxman Act seeks to stimulate competition by providing incentives to generic pharmaceutical manufacturers to introduce non-infringing forms of patented pharmaceutical products and to challenge patents on branded pharmaceutical products. If we are unsuccessful at challenging an Abbreviated New Drug Application (ANDA), filed pursuant to the Hatch-Waxman Act, cheaper generic versions of our products, which may be favored by insurers and third-party payors, may be launched commercially, which would significantly harm our business.

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FDA and foreign regulatory approval of our products is uncertain.

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

The process of obtaining FDA and other required regulatory approvals and clearances can take many years and will require us and our partners, as applicable, 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 or foreign regulatory approval varies depending on the product, the disease or condition that the product is in development for, and the requirements applicable to that particular product. The FDA or applicable foreign regulatory agency can delay, limit or deny approval of a product for many reasons, including that:

- a product may not be shown to be safe or effective;
- the FDA or foreign agency may interpret data from pre-clinical and clinical trials in different ways than we or our partners do;
- the FDA or foreign agency may not approve our or our partners manufacturing processes or facilities;
- a product may not be approved for all the indications we or our partners request;
- the FDA or foreign agency may change its approval policies or adopt new regulations;
- the FDA or foreign agency may not meet, or may extend, the Prescription Drug User Fee Act (PDUFA-V) date or its foreign equivalent with respect to a particular NDA or foreign application; and
- the FDA or foreign agency 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 or the applicable foreign agency, we or our partners may fail to obtain regulatory approval for our products.

Any delay or failure to obtain regulatory approvals for our products will result in increased costs, could diminish competitive advantages that we may attain and would adversely affect the marketing and sale of our products. Other than HETLIOZ® in the U.S. and the 31 countries in Europe covered by the centralized marketing authorization by the EC, and Fanapt® in the U.S., Mexico and Israel, we have not received, and may never receive, regulatory approval to

market any of our products in any jurisdiction.

Even following regulatory approval of our products, the FDA or the applicable foreign agency may impose limitations on the indicated uses for which such products may be marketed, subsequently withdraw approval or take other actions against us, our partners or such products that are adverse to our business. The FDA and foreign agencies generally approve 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, local and foreign 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 products. 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.

If our products 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 HETLIOZ® in January 2014 and the NDA for Fanapt® in May 2009, the EC s grant of the centralized marketing authorization for HETLIOZ® in July 2015, and the positive results of our completed trials for HETLIOZ® and Fanapt®, we are uncertain whether either of these products will ultimately prove to be effective and safe in humans long term and in all uses. 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 products, whether in clinical trials or commercially, may reveal that the product 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 products are determined to be unsafe or ineffective in humans, our business will be materially harmed.

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

Pre-clinical studies and clinical trials required to demonstrate the safety and efficacy of our products are time-consuming and expensive and together take several years to complete. Before obtaining regulatory approvals for the commercial sale of any of our products, we or our partners must demonstrate through preclinical testing and clinical trials that such product 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 products. Regulatory authorities may not permit us or our partners to undertake any additional clinical trials for our products, may force us to stop any ongoing clinical trials and it may be difficult to design efficacy studies for our products in new indications.

Clinical development efforts performed by us or our partners may not be successfully completed, or completed in a timely manner. 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 products and the size of the prospective patient population. Our ability to enroll patients in, and the commencement and rate of completion of, clinical trials for our products may be affected by many factors, including:

- the size and nature of the patient population;
- the design of the trial protocol for our clinical trials;
- the eligibility and exclusion criteria for the trial in question;
- the availability of competing therapies and competing clinical trials, and physician and patient perception of our product candidates and our other product candidates being studied in relation to these other potential options;
- the availability of raw materials and the possibility of raw materials expiring prior to their use;
- difficulty in maintaining contact with patients after treatment, resulting in incomplete data;
- poor effectiveness of our products during clinical trials;

unforeseen safety issues or side effects;

the number and location of clinical sites in our clinical trials;

the proximity and availability of clinical trial sites for prospective patients;

the availability of time and resources at the institutions where clinical trials are and will be conducted;

the availability of adequate financing to fund ongoing clinical trial expenses;

the study endpoints that rely on subjective patient reported outcomes; and

governmental or regulatory delays and changes in regulatory requirements and guidelines.

If we or our partners fail to complete successfully, or have difficulty enrolling a sufficient number of patients for, our clinical trials, we or they may not receive the regulatory approvals needed to market that product. Any such failure or difficulty could have a material adverse effect on our business.

Our products may cause undesirable side effects or have other properties that could delay, prevent or result in the revocation of their regulatory approval or limit their marketability.

Undesirable side effects caused by our products could interrupt, delay or halt clinical trials and could result in the denial of regulatory approval by the FDA or other regulatory authorities for any or all targeted indications, and in turn prevent us or our partners from commercializing or continuing the commercialization of such products and generating revenues from their sale. We will continue to assess the side effect profile of our products in ongoing clinical development programs. However, we cannot predict whether the commercial use of our approved products (or our products in development, if and when they are approved for commercial use) will produce undesirable or unintended side effects that have not been evident in the use of, or in clinical trials conducted for, such products to date. Additionally, incidents of product misuse may occur. These events, among others, could result in product recalls, product liability actions or withdrawals or additional regulatory controls, all of which could have a material adverse effect on our business, results of operations and financial condition.

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In addition, if after receiving marketing approval of a product, we, our partners or others identify undesirable side effects caused by such product, we or our partners could face one or more of the following:

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

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

We have a history of operating losses, anticipate future losses and may never become profitable on a sustained basis.

We have been engaged in identifying and developing products since March 2003, which has required, and will continue to require, significant research and development expenditures. The continued commercialization of HETLIOZ® and Fanapt® will require substantial additional expenditures.

As of December 31, 2017, we had an accumulated deficit of $361.4 million and we cannot estimate with precision the extent of our future losses. In April 2014, we commercially launched HETLIOZ® in the U.S. for the treatment of Non-24 and in August 2016 we commercially launched HETLIOZ® in Germany for the treatment of Non-24 in totally blind adults. We are currently evaluating the commercial opportunity for HETLIOZ® in the rest of Europe. In December 2014, we acquired all rights to Fanapt® from Novartis. The continued commercialization of HETLIOZ® and Fanapt® will require substantial additional expenditures. Novartis launched Fanapt® in the U.S. in the first quarter of 2010 and we began selling Fanapt® on our own in the first quarter of 2015. We may not succeed in gaining additional market acceptance of Fanapt® in the U.S. and we may not succeed in commercializing HETLIOZ® or Fanapt® outside of the U.S. We may not be profitable even if our products are successfully commercialized. We may be unable to fully develop, obtain regulatory approval for, commercialize, manufacture, market, sell and derive revenue from our products in the timeframes we project, if at all, and our inability to do so would materially and adversely impact the market price of our common stock and our ability to raise capital and continue operations.

There can be no assurance that we will achieve sustained profitability. Our ability to achieve sustained profitability in the future depends, in part, upon:

- our ability to obtain and maintain regulatory approval for our products, particularly HETLIOZ® for the treatment of Non-24, both in the U.S. and in foreign countries;

our level of success in commercializing HETLIOZ® in the U.S., Europe and other jurisdictions in which HETLIOZ® may receive regulatory approval, if any;

our level of success in raising awareness regarding Non-24 in the medical and patient communities;

our level of success in marketing and selling Fanapt® in the U.S. and our or our partners level of success in marketing and selling Fanapt® in Israel and other jurisdictions in which we may receive regulatory approval, if any;

our ability to enter into and maintain agreements to develop and commercialize our products;

our and our partners ability to develop, have manufactured and market our products;

our and our partners ability to obtain adequate reimbursement coverage for our products from insurance companies, government programs and other third party payors; and

our ability to obtain additional research and development funding from collaborative partners or funding for our products.

In addition, the amount we spend will impact our profitability. Our spending will depend, in part, upon:

the costs of our marketing or awareness campaigns;

the progress of our research and development programs for our products, including clinical trials;

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- the time and expense that will be required to pursue FDA and/or foreign regulatory approvals for our products and whether such approvals are obtained on a timely basis, if at all;
- the time and expense required to prosecute, enforce and/or challenge patent and other intellectual property rights;
- the cost of third party manufacturers;
- the number of additional products we pursue;
- how competing technological and market developments affect our products;
- the cost of possible acquisitions of technologies, products, product rights or companies;
- the cost of obtaining licenses to use technology owned by others for proprietary products and otherwise;
- the costs and effects of potential litigation; and
- the costs associated with recruiting and compensating a highly skilled workforce in an environment where competition for such employees may be intense.

We may not achieve all or any of these goals and, thus, we cannot provide assurances that we will ever be profitable on a sustained basis or achieve significant revenues. Even if we do achieve some or all of these goals, we may not achieve significant or sustained commercial success.

Our ability to use net operating loss carryforwards and tax credit carryforwards to offset future taxable income may be limited as a result of transactions involving our common stock.

In general, under Section 382 of the Internal Revenue Code of 1986, as amended (IRC), a corporation that undergoes an ownership change is subject to limitations on its ability to utilize its pre-change net operating losses (NOLs) and certain other tax assets (tax attributes) to offset future taxable income. In general, an ownership change occurs if the aggregate stock ownership of certain stockholders increases by more than 50 percentage points over such stockholders lowest percentage ownership during the testing period (generally three years). Transactions involving our common stock, even those outside our control, such as purchases or sales by investors, within the testing period could result in an ownership change. A limitation on our ability to utilize some or all of our NOLs or credits could have a material adverse effect on our results of operations and cash flows. Ownership changes occurred in the years ending December 31, 2014 and 2008. We believe that the ownership changes in 2014 and 2008 will not impact our ability to utilize NOL and credit carryforwards; however, future ownership changes may cause our existing tax attributes to have additional limitations.

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 with third parties on terms that may not be attractive to us.

Our activities will necessitate significant uses of working capital throughout 2018 and beyond. It is uncertain whether our existing funds will be sufficient to meet our operating needs. As of December 31, 2017, our total cash and cash equivalents and marketable securities were $143.4 million. Our long term capital requirements are expected to depend on many factors, including, among others:

our level of success in commercializing HETLIOZ® and Fanapt® globally;

outcomes of ongoing and potential patent litigation;

costs of developing and maintaining sales, marketing and distribution channels and our ability to sell our products;

market acceptance of our products;

costs involved in establishing manufacturing capabilities for commercial quantities of our products;

the number of potential formulations and products 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;

costs for recruiting and retaining employees and consultants;

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costs for training physicians; and

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

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, 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 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.

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

Our arrangements with contract research organizations are critical to our success in bringing our products to the market and promoting such marketed products profitably. We are dependent on contract research organizations, third-party vendors and investigators for pre-clinical testing and clinical trials related to our drug discovery and development efforts and we will likely continue to depend on them to assist in our future discovery and development efforts. These parties are not our employees and we cannot control the amount or timing of resources that they devote to our programs. As such, they may not complete activities on schedule or may not conduct our clinical trials in accordance with regulatory requirements or our stated protocols. The parties with which we contract for execution of our clinical trials play a significant role in the conduct of the trials and the subsequent collection and analysis of data. If they fail to devote sufficient time and resources to our drug development programs or if their performance is substandard, it will delay the development, approval and commercialization of our products. Moreover, these parties may also have relationships with other commercial entities, some of which may compete with us. If they assist our competitors, it could harm our competitive position.

Our contract research organizations could merge with or be acquired by other companies or experience financial or other setbacks unrelated to our collaboration that could, nevertheless, materially adversely affect our business, results of operations and financial condition.

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

We rely on a limited number of third party manufacturers to formulate and manufacture our products and our business will be seriously harmed if these manufacturers are not able to satisfy our demand and alternative sources are not available.

Our expertise is primarily in the research and development and pre-clinical and clinical trial phases of product development. We do not have an in-house manufacturing capability and depend completely on a small number of third-party manufacturers and active pharmaceutical ingredient formulators for the manufacture of our products. Therefore, we are dependent on third parties for our formulation development and manufacturing of our products. This may expose us to the risk of not being able to directly oversee the production and quality of the manufacturing process and provide ample commercial supplies to successfully launch and maintain the marketing of our products. Furthermore, these third party contractors, whether foreign or domestic, may experience regulatory compliance difficulty, mechanical shut downs, employee strikes, or other unforeseeable events that may delay or limit production. Our inability to adequately establish, supervise and conduct (either ourselves or through third parties) all aspects of the formulation and manufacturing processes would have a material adverse effect on our ability to develop and commercialize our products.

We have agreements in place with Patheon Pharmaceuticals Inc. and Patheon Inc. (collectively, Patheon), subsidiaries of Thermo Fisher Scientific, for the manufacture of HETLIOZ® and Fanapt®.

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In January 2014, we entered into a manufacturing agreement with Patheon for the manufacture of commercial supplies of HETLIOZ® 20 mg capsules at Patheon s Cincinnati, Ohio manufacturing site. In May 2016, we entered into a manufacturing agreement with Patheon for the manufacture of commercial supplies of Fanapt® capsules tablets at Patheon s Mississauga, Ontario, Canada manufacturing site. We do not have exclusive long-term agreements with any other third party manufacturers of our products. If our current manufacturers, or any other third party manufacturer, is unable or unwilling to perform its obligations under our manufacturing agreements for any reason, we may not be able to locate alternative acceptable manufacturers or formulators or enter into favorable agreements with them. Any inability to acquire sufficient quantities of our products in a timely manner from these third parties could adversely affect sales of our products, delay clinical trials and prevent us from developing our products in a cost-effective manner or on a timely basis. In addition, manufacturers of our products are subject to cGMP and similar foreign standards and we do not have control over compliance with these regulations by our manufacturers. If one of our contract manufacturers fails to maintain compliance, the production of our products could be interrupted, resulting in delays and additional costs. In addition, if the facilities of such manufacturers do not pass a pre-approval or post-approval plant inspection, the FDA will not grant approval and may institute restrictions on the marketing or sale of our products.

Our manufacturing strategy presents the following additional risks:

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

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

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

We and our partners rely on manufacturers to purchase from third-party suppliers the materials necessary to produce our products for clinical trials and commercialization. Suppliers may not sell these materials to such manufacturers at the times we or our partners need them or on commercially reasonable terms. We do not have any control over the process or timing of the acquisition of these materials by these manufacturers. Moreover, we currently do not have any agreements for the commercial production of these materials. If the manufacturers are unable to obtain these materials for our or our partners clinical trials, product testing, potential regulatory approval of our products and commercial scale manufacturing could be delayed, significantly affecting our and our partners ability to further develop and commercialize our products. If we, our manufacturers or our partners, as applicable, are unable to purchase these materials for our products, there would be a shortage in supply or the commercial launch of such products would be delayed, which would materially and adversely affect our or our partners ability to generate revenues from the sale of such products.

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

A component of our business strategy is acquiring rights to develop and commercialize products discovered or developed by other pharmaceutical and biotechnology companies for which we may find effective uses and markets through our unique pharmacogenetics and pharmacogenomics expertise for the treatment of central nervous system

disorders. Competition for the acquisition of these products is intense. If we are not able to identify opportunities to acquire rights to commercialize additional products, we may not be able to develop a diverse portfolio of products and our business may be harmed. Additionally, it may take substantial human and financial resources to secure commercial rights to promising products. Moreover, if other firms develop pharmacogenetics and pharmacogenomics capabilities, we may face increased competition in identifying and acquiring additional products.

We may not be successful in the development of products for our own account.

In addition to our business strategy of acquiring rights to develop and commercialize products, we may develop products for our own account by applying our technologies to off-patent drugs as well as developing our own proprietary molecules. Because we will be funding the development of such programs, there is a risk that we may not be able to continue to fund all such programs to completion or to provide the support necessary to perform the clinical trials, obtain regulatory approvals or market any approved products. We expect the development of products for our own account to consume substantial resources. If we are able to develop commercial products on our own, the risks associated with these programs may be greater than those associated with our programs with collaborative partners.

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

We are highly dependent on principal members of our management team and scientific staff, including our Chief Executive Officer, Mihael H. Polymeropoulos, M.D. These executives each have significant pharmaceutical industry experience. The loss of any such executives, including Dr. Polymeropoulos, or any other principal member of our management team or scientific staff, would impair our ability to identify, develop and market new products. Our management and other employees may voluntarily terminate their employment with us at any time. The loss of the services of these or other key personnel, or the inability to attract and retain additional qualified personnel, could result in delays to development or approval, loss of sales and diversion of management resources. In addition, we depend on our ability to attract and retain other highly skilled personnel, including research scientists. Competition for qualified personnel is intense, and the process of hiring and integrating such qualified personnel is often lengthy. We may be unable to recruit such personnel on a timely basis, if at all, which would negatively impact our development and commercialization programs.

Additionally, we do not currently maintain key person life insurance on the lives of our executives or any of our employees. This lack of insurance means that we may not have adequate compensation for the loss of the services of these individuals.

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

The risk that we may be sued on product liability claims is inherent in the development and sale of pharmaceutical products. For example, we face a risk of product liability exposure related to the testing of our products in clinical trials and will face even greater risks upon commercialization by us or our partners of our products. We believe that we may be at a greater risk of product liability claims relative to other pharmaceutical companies because our products are intended to treat central nervous system disorders, and it is possible that we may be held liable for the behavior and actions of patients who use our products. These lawsuits may divert our management from pursuing our business strategy and may be costly to defend. In addition, if we are held liable in any of these lawsuits, we may incur substantial liabilities and we or our partners may be forced to limit or forego further commercialization of one or more of our products. Although we maintain product liability insurance, our aggregate coverage limit under this insurance is $30.0 million, and while we believe this amount of insurance is sufficient to cover our product liability exposure, these limits may not be high enough to fully cover potential liabilities. As our development activities and commercialization efforts progress and we and our partners sell our products, this coverage may be inadequate, we may be unable to obtain adequate coverage at an acceptable cost or we may be unable to get adequate coverage at all or our insurer may disclaim coverage as to a future claim. This could prevent the commercialization or limit the commercial potential of our products. Even if we are able to maintain insurance that we believe is adequate, our results of operations and financial condition may be materially adversely affected by a product liability claim. Uncertainties resulting from the initiation and continuation of products liability litigation or other proceedings could have a material adverse effect on our ability to compete in the marketplace. Product liability litigation and other related proceedings may also require significant management time.

E.U. Member States tend to impose strict price controls, which may delay or prevent the further commercial launch or impede the commercial success of HETLIOZ® in Europe and adversely affect our future results of operations.

In the E.U., prescription drug pricing and reimbursement are subject to governmental control and reimbursement mechanisms used by private and public health insurers in the E.U. vary by Member State. For the public systems, reimbursement is determined by guidelines established by the legislature or responsible national authority. As

elsewhere, inclusion in reimbursement catalogues focuses on the medical usefulness, need, quality and economic benefits to patients and the health care system. Acceptance for reimbursement comes with cost, use and often volume restrictions, which can vary by Member State. Although we have received marketing authorization for HETLIOZ® from the EC, pricing negotiations with governmental authorities may take a considerable amount of time in those Member States that impose price controls. For example, we launched HETLIOZ® commercially in Germany in August 2016, and concluded our pricing negotiations with German authorities in October 2017. In addition, to obtain reimbursement or pricing approval for HETLIOZ® in some Member States, we may be required to conduct a clinical trial that compares the cost-effectiveness of HETLIOZ®, to other available therapies.

Some Member States require approval of the sale price of a drug before it can be marketed. In many countries, the pricing review period begins after marketing or product licensing approval is granted. In some Member States, prescription pharmaceutical pricing remains subject to continuing governmental control even after initial approval is granted. As a result, we may be subject to lengthy price regulations that delay or prevent the commercial launch of HETLIOZ® in a particular Member State and negatively impact the revenues that are generated from the sale of HETLIOZ® in that country. If reimbursement of HETLIOZ® is unavailable or limited in scope or amount, or if pricing for HETLIOZ® is set at unsatisfactory levels or takes too long to establish, or if there is competition from lower priced cross-border sales, our results of operations will be negatively affected.

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We may not be able to effectively market and sell our future products, if approved, in the U.S.

We plan to continue to build our sales and marketing capabilities in the U.S. to commercialize future products, if approved. Our current sales and marketing capabilities in the U.S. may not be adequate to support the commercialization of future products and we would expect to build such capabilities by investing significant amounts of financial and management resources. Furthermore, the cost of establishing and maintaining marketing and sales capabilities may not be justifiable in light of the revenues generated by any future products.

If we are unable to establish and maintain adequate sales and marketing capabilities for future products or are unable to do so in a timely manner, we may not be able to generate product revenues from these products which may prevent us from reaching or maintaining profitability.

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

PPACA substantially changes the way healthcare is financed by both governmental and private insurers, and significantly impacts the pharmaceutical industry. PPACA contains a number of provisions that are expected to impact our business and operations, in some cases in ways we cannot currently predict. Changes that may affect our business if we or our partners commercialize our products in the future include those governing enrollment in federal healthcare programs, reimbursement changes, rules regarding prescription drug benefits under the health insurance exchanges, and fraud and abuse and enforcement. In addition, continued implementation of PPACA may result in the expansion of new programs such as Medicare payment for performance initiatives, and may impact existing government healthcare programs, such as by improving the physician quality reporting system and feedback program.

Additional provisions of PPACA may negatively affect our revenues from products that we or our partners commercialize in the future. For example, as part of PPACA s provisions closing a coverage gap that currently exists in the Medicare Part D prescription drug program, manufacturers of branded prescription drugs are required to provide a 50% discount on branded prescription drugs dispensed to beneficiaries within this coverage gap. Medicare Part D is a prescription drug benefit available to all Medicare beneficiaries. It is a voluntary benefit that is implemented through private plans under contractual arrangements with the federal government. Similar to pharmaceutical coverage through private health insurance, Part D plans negotiate discounts from drug manufacturers and pass on some of those savings to Medicare beneficiaries. PPACA also makes changes to the Medicaid Drug Rebate Program, discussed in more detail below, including increasing the minimum rebate from 15.1% to 23.1% of the average manufacturer price for most innovator products. On February 1, 2016, CMS, the federal agency that administers the Medicare and Medicaid programs, issued final regulations to implement the changes to the Medicaid Drug Rebate Program under PPACA. These regulations became effective on April 1, 2016.

Many of PPACA s most significant reforms did not take effect until 2014 or thereafter, and the resulting new programs and requirements will continue to evolve in the next few years. Some states have chosen not to expand their Medicaid programs by raising the income limit to 133% of the federal poverty level. In part because not all states have expanded their Medicaid programs, it is unclear whether there will be more uninsured patients than anticipated when Congress passed PPACA. For each state that has opted not to expand its Medicaid program, there will be fewer insured patients overall. An increase in the proportion of uninsured patients who are prescribed products resulting from our proprietary or partnered programs could impact the future sales of any products that are commercialized in the future and our business and results of operations.

Further, in September 2007, the Food and Drug Administration Amendments Act of 2007 was enacted giving the FDA enhanced post-marketing authority including the authority to require post-marketing studies and clinical trials,

labeling changes based on new safety information and compliance with Risk Evaluation and Mitigation Strategy (REMS) approved by the FDA. The FDA s exercise of this authority could result in delays or increased costs during product development, clinical trials and regulatory review, increased costs to ensure compliance with post-approval regulatory requirements and potential restrictions on the sale and/or distribution of approved products.

In addition, other legislative changes have been proposed and adopted in the U.S. since PPACA was enacted. On August 2, 2011, the Budget Control Act of 2011 among other things, created measures for spending reductions by Congress. A Joint Select Committee on Deficit Reduction, tasked with recommending a targeted deficit reduction of at least $1.2 trillion for the years 2013 through 2021, was unable to reach required goals, thereby triggering the legislation s automatic reduction to several government programs. This includes aggregate reductions to Medicare payments to providers of up to 2% per fiscal year, starting in 2013, which will remain in effect until 2024 unless additional congressional action is taken. On January 2, 2013, the American Taxpayer Relief Act of 2012 was signed into law, which, among other things, increased the statute of limitations period for the government to recover overpayments to providers from three to five years. We expect that additional federal healthcare reform measures will be adopted in the future, any of which could limit the amounts that federal and state governments will pay for healthcare products and services, and in turn could significantly reduce the projected value of certain development projects and reduce our profitability.

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More recently, the current presidential administration and many members of the U.S. Congress have attempted to repeal and replace PPACA, but they have been unsuccessful in doing so as of the date of the filing of this report. We cannot predict the ultimate form or timing of any repeal or replacement of PPACA or the effect such repeal or replacement would have on our business. Regardless of the impact of repeal or replacement of PPACA on us, the government has shown significant interest in pursuing healthcare reform and reducing healthcare costs.

We expect that additional state and federal healthcare reform measures will be adopted in the future, any of which could limit the amounts that federal and state governments will pay for healthcare products and services, which could result in reduced demand for our products once approved or additional pricing pressures, and may adversely affect our operating results.

Significant developments arising from changes in the political climate could have a material adverse effect on us.

Changes in U.S. social, political, regulatory and economic conditions or in laws and policies governing foreign trade, manufacturing, development and investment, and any negative sentiments towards the U.S. as a result of such changes, could adversely affect our business.

Additionally, in June 2016, the United Kingdom (U.K.) held a referendum and voted in favor of leaving the E.U. In February 2017, the U.K. parliament voted to allow the U.K. to exit the E.U. by passing a bill that gives the prime minister of the U.K. the authority to invoke Article 50 of the Lisbon Treaty. This referendum has created political and economic uncertainty, particularly in the U.K. and the E.U., and this uncertainty may last for years. There are many ways in which our business could be affected, only some of which we can identify.

The referendum, and the likely withdrawal of the U.K. from the E.U. it triggers, has caused and, along with events that could occur in the future as a consequence of the U.K. s withdrawal, including the possible breakup of the U.K., may continue to cause significant volatility in global financial markets, including in global currency and debt markets. This volatility could cause a slowdown in economic activity in the U.K., Europe or globally, which could adversely affect our operating results and growth prospects. In addition, our business could be negatively affected by new trade agreements between the U.K. and other countries, including the U.S., and by the possible imposition of trade or other regulatory barriers in the U.K., especially if the U.K. withdraws from the E.U. These possible negative impacts, and others resulting from the U.K. s actual or threatened withdrawal from the E.U., may adversely affect our operating results and growth prospects as well as the manner in which we conduct our business operations in Europe.

U.S. federal income tax reform could adversely affect us.

In December 2017, U.S. federal tax legislation, commonly referred to as the Tax Cuts and Jobs Act (TCJA), was signed into law, significantly reforming the Internal Revenue Code of 1986, as amended (IRC). The TCJA, among other things, includes changes to U.S. federal tax rates, imposes significant additional limitations on the deductibility of interest, allows for the expensing of capital expenditures, puts into effect the migration from a worldwide system of taxation to a territorial system and modifies or repeals many business deductions and credits.

We continue to examine the impact the TCJA may have on our business. The TCJA is a far-reaching and complex revision to the U.S. federal income tax laws with disparate and, in some cases, countervailing impacts on different categories of taxpayers and industries, and will require subsequent rulemaking and interpretation in a number of areas. The long-term impact of the TCJA on the overall economy, the industries in which we operate and our and our partners business cannot be reliably predicted at this early stage of the new law s implementation. There can be no assurance that the TCJA will not negatively impact our operating results, financial condition, and future business operations. The estimated impact of the TCJA is based on our management s current knowledge and assumptions,

following consultation with our tax advisors. Because of our valuation allowance in the U.S., ongoing tax effects of the Act are not expected to materially change our effective tax rate in future periods. The impact of the TCJA on holders of common stock is uncertain and could be materially adverse. This Annual Report does not discuss any such tax legislation or the manner in which it might affect investors in common stock. Investors should consult with their own tax advisors with respect to such legislation and the potential tax consequences of investing in common stock.

New legislation or regulation which could affect our tax burden could be enacted by any governmental authority. We cannot predict the timing or extent of such tax-related developments which could have a negative impact on our financial results. Additionally, we use our best judgment in attempting to quantify and reserve for these tax obligations. However, a challenge by a taxing authority, our ability to utilize tax benefits such as carryforwards or tax credits, or a deviation from other tax-related assumptions may cause actual financial results to deviate from previous estimates.

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Future transactions may harm our business or the market price of our stock.

We regularly review potential transactions related to technologies, products or product rights and businesses complementary to our business. These transactions could include:

- mergers;
- acquisitions;
- strategic alliances;
- licensing agreements; and
- co-promotion and similar agreements.

We may choose to enter into one or more of these transactions at any time, which may cause substantial fluctuations in the market price of our stock. Moreover, depending upon the nature of any transaction, we may experience a charge to earnings, which could also materially adversely affect our results of operations and could harm the market price of our stock.

We may undertake strategic acquisitions in the future, and difficulties integrating such acquisitions could damage our ability to achieve or sustain profitability.

Although we have no experience in acquiring businesses, we may acquire businesses or assets that complement or augment our existing business. If we acquire businesses with promising products or technologies, we may not be able to realize the benefit of acquiring such businesses if we are unable to move one or more products through preclinical and/or clinical development to regulatory approval and commercialization. Integrating any newly acquired businesses or technologies could be expensive and time-consuming, resulting in the diversion of resources from our current business. We may not be able to integrate any acquired business successfully. We cannot assure you that, following an acquisition, we will achieve revenues, specific net income or loss levels that justify the acquisition or that the acquisition will result in increased earnings, or reduced losses, for the combined company in any future period. Moreover, we may need to raise additional funds through public or private debt or equity financing to acquire any businesses, which would result in dilution for stockholders or the incurrence of indebtedness and may not be available on terms which would otherwise be acceptable to us. We may not be able to operate acquired businesses profitably or otherwise implement our growth strategy successfully.

Our operating results may fluctuate significantly due to a number of factors which make our future results difficult to predict and could cause our operating results to fall below expectations or our guidance.

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

product sales;

cost of product sales;

marketing and other expenses;

manufacturing or supply issues;

the timing and amount of royalties or milestone payments;

our addition or termination of development programs;

variations in the level of expenses related to our products or future development programs;

regulatory developments affecting our products or those of our competitors; our execution of collaborative, licensing or other arrangements, and the timing of payments we may make or receive under these arrangements;

any intellectual property infringement or other lawsuit in which we may become involved; and

the timing and recognition of stock-based compensation expense.

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

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We are increasingly dependent on information technology systems, infrastructure and data. Cybersecurity breaches could expose us to liability, damage our reputation, compromise our confidential information or otherwise adversely affect our business.

We are increasingly dependent upon information technology systems, infrastructure and data. Our computer systems may be vulnerable to service interruption or destruction, malicious intrusion and random attack. Security breaches pose a risk that sensitive data, including intellectual property, trade secrets or personal information may be exposed to unauthorized persons or to the public. Cyber-attacks are increasing in their frequency, sophistication and intensity, and have become increasingly difficult to detect. Cyber-attacks could include the deployment of harmful malware, denial-of service, social engineering and other means to affect service reliability and threaten data confidentiality, integrity and availability. Our key business partners face similar risks, and a security breach of their systems could adversely affect our security posture. While we continue to invest in data protection and information technology, there can be no assurance that our efforts will prevent service interruptions, or identify breaches in our systems, that could adversely affect our business and operations and/or result in the loss of critical or sensitive information, which could result in financial, legal, business or reputational harm.

Risks related to intellectual property and other legal matters

Our rights to develop and commercialize our products are subject in part to the terms and conditions of licenses or sublicenses granted to us by other pharmaceutical companies.

Our rights to our product portfolio are based in part on patents and other intellectual property licensed from third-parties. These third parties may generally terminate the license agreements under certain circumstances, including a material breach of the agreement by the other. In the event we terminate our license, or if the third-party terminates our license due to our breach, rights to the intellectual property revert back to the licensor. Any termination or reversion of our rights to develop or commercialize our products would have a material adverse effect on our business.

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

Method of treatment patents protect the use of a product for the method specified in the patent claims. This type of patent does not prevent a competitor from making and marketing a product that is identical to our product for a use that is outside the scope of the patented method. Moreover, even if competitors do not actively promote their product for our patented methods, physicians may prescribe these products off-label. Although off-label prescriptions may infringe or contribute to the infringement of method of treatment patents, such infringement may be difficult to prevent.

Our patents and patent applications may be challenged or fail to result in issued patents and our existing or future patents may be too narrow to prevent third parties from developing or designing around these patents. In addition, we generally rely on trade secret protection and confidentiality agreements to protect certain proprietary know-how that is not patentable, for processes for which patents are difficult to enforce and for any other elements of our drug development processes that involve proprietary know-how, information and technology that is not covered by patent applications. While we require all of our employees, consultants, advisors and any third parties who have access to our proprietary know-how, information and technology to enter into confidentiality agreements, we cannot be certain that this know-how, information and technology will not be disclosed or that competitors will not otherwise gain access to our trade secrets or independently develop substantially equivalent information and techniques. Further, the laws of some foreign countries do not protect proprietary rights to the same extent as the laws of the U.S. As a result, we may

encounter significant problems in protecting and defending our intellectual property both in the U.S. and abroad. If we are unable to protect or defend the intellectual property related to our technologies, we will not be able to establish or maintain a competitive advantage in our market.

We have been, and may continue to be, involved in lawsuits to protect or enforce our patents, which could be expensive, time-consuming and unsuccessful, and third parties may challenge the validity or enforceability of our patents and they may be successful.

Even where laws provide protection or we are able to obtain patents, costly and time-consuming litigation may be necessary to enforce and determine the scope of our proprietary rights, and the outcome of such litigation would be uncertain. Moreover, any actions we may bring to enforce our intellectual property against our competitors could provoke them to bring counterclaims against us, and some of our competitors have substantially greater intellectual property portfolios than we have. To counter infringement or unauthorized use of any patents we may obtain, we may be required to file infringement claims, which can be expensive and time-consuming to litigate. In addition, if we or one of our future collaborators were to initiate legal proceedings against a third party to enforce a patent covering one of our products, current product candidates, or one of our future products, the defendant could counterclaim that the patent is invalid or unenforceable. In patent litigation in the U.S., defendant counterclaims alleging invalidity or

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unenforceability are commonplace and challenges to validity of patents in certain foreign jurisdictions are common as well. Grounds for a validity challenge could be an alleged failure to meet any of several statutory requirements, including lack of novelty, obviousness, non-enablement or lack of statutory subject matter. Grounds for an unenforceability assertion could be an allegation that someone connected with prosecution of the patent withheld relevant material information from the U.S. Patent and Trademark Office, or made a materially misleading statement, during prosecution. We may assert the patents in Hatch-Waxman litigation against the party filing the ANDA to keep the competing product off of the market until the patents expire but there is a risk that we will not succeed. The party filing the ANDA may also counterclaim in the litigation that our patents are not valid or unenforceable, and the court may find one or more claims of our patents invalid or unenforceable. If this occurs, a competing generic product could be marketed prior to expiration of our patents listed in the FDA s *Approved Drug Products with Therapeutic Equivalence Evaluations*, commonly known as the Orange Book, which would harm our business.

In June 2014, we filed suit against Roxane Laboratories, Inc. (Roxane) in the U.S. District Court for the District of Delaware (Delaware District Court). The suit seeks an adjudication that Roxane has infringed one or more claims of our U.S. Patent No. 8,586,610 (610 Patent) by submitting to the FDA an ANDA for a generic version of Fanapt® prior to the expiration of the 610 Patent in November 2027. In addition, pursuant to a settlement agreement with Novartis Pharma AG (Novartis), we assumed Novartis patent infringement action against Roxane in the Delaware District Court. That suit alleges that Roxane has infringed one or more claims of U.S. Patent RE39198 (198 Patent), which is licensed exclusively to us, by filing an ANDA for a generic version of Fanapt® prior to the expiration of the 198 Patent in November 2016. These two cases against Roxane were consolidated by agreement of the parties and were tried together in a five-day bench trial that concluded on March 4, 2016. On August 25, 2016, the Delaware District Court ruled in our favor, finding that Roxane s ANDA product infringed the asserted claims of the 610 Patent and the 198 Patent. The Delaware District Court ruled that we are entitled to a permanent injunction against Roxane enjoining Roxane from infringing the 610 Patent, including the manufacture, use, sale, offer to sell, sale, distribution or importation of any generic iloperidone product described in the 610 Patent ANDA until the expiration of the 610 Patent in November 2027. If we obtain pediatric exclusivity, the injunction against Roxane would be extended until May 2028 under the Delaware District Court s order. On September 23, 2016, Roxane filed a notice of appeal with the Federal Circuit Court of Appeals (Federal Circuit). Roxane filed its opening appellate brief on February 7, 2017. We filed our responsive brief on April 19, 2017, and Roxane filed its reply brief on May 3, 2017. On July 27, 2017, Roxane, now a subsidiary of Hikma Pharmaceuticals PLC (Hikma), petitioned the Federal Circuit to substitute Roxane with new defendants West-Ward Pharmaceuticals International Limited and West-Ward Pharmaceuticals Corp. (each of which is a subsidiary of Hikma and both of which are referred to collectively herein as West-Ward). We did not oppose the substitution of West-Ward for Roxane. The appeal is fully briefed, and oral argument was held on December 5, 2017. The Federal Circuit has not yet issued a decision.

In 2015, we filed six separate patent infringement lawsuits in the Delaware District Court against Roxane, Inventia Healthcare Pvt. Ltd. (Inventia), Lupin Ltd. and Lupin Pharmaceuticals, Inc. (Lupin), Taro Pharmaceuticals USA, Inc. and Taro Pharmaceutical Industries, Ltd. (Taro), and Apotex Inc. and Apotex Corp. (collectively, the Defendants). The lawsuits each seek an adjudication that the respective Defendants infringed one or more claims of the 610 Patent and/or our U.S. Patent No. 9,138,432 (432 Patent) by submitting to the FDA an ANDA for a generic version of Fanapt® prior to the expiration of the 610 Patent in November 2027 or the 432 Patent in September 2025. The Defendants have denied infringement and counterclaimed for declaratory judgment of invalidity and noninfringement of the 610 Patent and the 432 Patent. Certain Defendants have since entered into agreements resolving these lawsuits, as discussed below. The remaining parties have agreed, and the Delaware District Court has ordered, that within 14 days after any decision on the merits in the Roxane appeal, the parties will submit to the Delaware District Court a status report and request a schedule for trial. We entered into a confidential stipulation with Inventia regarding any potential launch of Inventia s generic ANDA product. We also entered into a confidential stipulation with Lupin regarding any potential launch of Lupin s generic ANDA product.

Lupin filed counter-claims for declaratory judgment of invalidity and noninfringement of seven of our method of treatment patents that are listed in the Orange Book related to Fanapt® (such seven patents, the Method of Treatment Patents). We have not sued Lupin for infringing the Method of Treatment Patents. On October 13, 2016, we, along with Lupin, filed a Stipulation of Dismissal in the Delaware District Court pursuant to which Lupin s counterclaims relating to the Method of Treatment Patents were dismissed without prejudice in recognition of an agreement reached between Lupin and us by which we would not assert those patents against Lupin absent certain changes in Lupin s proposed prescribing information for its iloperidone tablets.

On October 24, 2016, we entered into a License Agreement with Taro to resolve our patent litigation against Taro regarding Taro s ANDA seeking approval of its generic version of Fanapt® (Taro License Agreement). Under the Taro License Agreement, we granted Taro a non-exclusive license to manufacture and commercialize Taro s version of Fanapt® in the U.S. effective November 2, 2027, unless prior to that date we obtain pediatric exclusivity for Fanapt®, in which case, the license will be effective May 2, 2028. Taro may enter the market earlier under certain limited circumstances. The Taro License Agreement, which is subject to review by the U.S. Federal Trade Commission (FTC) and the U.S. Department of Justice (DOJ), provides for a full settlement and release by us and Taro of all claims that are the subject of the litigation.

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On December 7, 2016, we entered into a License Agreement with Apotex to resolve our patent litigation against Apotex regarding Apotex s ANDA seeking approval of its generic version of Fanapt® (Apotex License Agreement). Under the Apotex License Agreement, we granted Apotex a non-exclusive license to manufacture and commercialize Apotex s version of Fanapt® in the U.S. effective November 2, 2027, unless prior to that date we obtain pediatric exclusivity for Fanapt®, in which case, the license will be effective May 2, 2028. Apotex may enter the market earlier under certain limited circumstances. The Apotex License Agreement, which is subject to review by the FTC and the DOJ, provides for a full settlement and release by us and Apotex of all claims that are the subject of the litigation.

On February 26, 2016, Roxane filed suit against us in the U.S. District Court for the Southern District of Ohio (Ohio District Court). The suit sought a declaratory judgment of invalidity and noninfringement of the Method of Treatment Patents. We have not sued Roxane for infringing the Method of Treatment Patents. We filed a motion to dismiss this lawsuit for lack of personal jurisdiction or to transfer the lawsuit to the Delaware District Court. On December 20, 2016, the Ohio District Court ruled in our favor, dismissing Roxane s suit without prejudice for lack of personal jurisdiction.

On February 26, 2016, Roxane filed a Petition for *Inter Partes* Review (IPR) of the 432 Patent with the Patent Trials and Appeals Board (PTAB) of the U.S. Patent and Trademark Office. We filed a Preliminary Response on June 7, 2016, and on August 30, 2016, the PTAB denied the request by Roxane to institute an IPR of the 432 Patent. On September 29, 2016, Roxane filed a Petition for Rehearing with the PTAB, and on October 13, 2016, we filed a Response to Roxane s Petition. On November 4, 2016, the PTAB denied Roxane s Petition for Rehearing.

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

The Hatch-Waxman Act provides for an extension of patent term for drugs for a period of up to five years to compensate for time spent in development. Assuming we gain a five-year patent term extension for HETLIOZ®, and that we continue to have rights under our license agreement with respect to this product, we would have exclusive rights to the HETLIOZ® U.S. new chemical entity patent (the primary patent covering the product as a new composition of matter) until 2022. We also own HETLIOZ® U.S. method of treatment patents (directed to the approved method of treatment as described in the HETLIOZ® label approved by the FDA), which expire normally in 2033 and 2034. The Fanapt® U.S. new chemical entity patent received the full five-year patent term extension under the Hatch-Waxman Act and so this patent in the U.S. expired in November 2016. In November 2013, a patent directed to a method of treating patients with Fanapt® based on genotype was issued to us by the U.S. Patent and Trademark Office. This patent, which was listed in the Orange Book in January 2015, is set to expire in 2027. Please see the risk factor entitled We have been, and may be, involved in lawsuits to protect or enforce our patents, which could be expensive, time-consuming and unsuccessful, and third parties may challenge the validity or enforceability of our patents and they may be successful, and Part I, Item 3, *Legal Proceedings,* of this annual report on Form 10-K for additional information. See also Note 16, *Legal Matters*, to the consolidated financial statements included in Part II of this annual report on Form 10-K for additional information. Eight additional U.S. patents directed to methods of treating patients with Fanapt®, which are set to expire between 2025 and 2031, were issued to us in 2015.

A directive in the E.U. provides that companies that receive regulatory approval for a new medicinal product will have a 10-year period of market exclusivity for that product (with the possibility of a further one-year extension), beginning on the date of such European regulatory approval, regardless of when the European new chemical entity patent covering such product expires. A generic version of the approved drug may not be marketed or sold in Europe during such market exclusivity period. This directive is of material importance with respect to Fanapt®, since the European new chemical entity patent for Fanapt® has expired.

Assuming we gain a five-year patent term restoration for tradipitant, and that we continue to have rights under our license agreement with respect to this product, we would have exclusive rights to tradipitant s U.S. new chemical entity patent until 2029. Assuming we gain a five-year patent term restoration for VQW-765, and that we continue to have rights under our license agreement with respect to this product, we would have exclusive rights to VQW-765 s U.S. new chemical entity patent until 2028.

However, there is no assurance that we will receive the extensions of our patents or other exclusive rights available under the Hatch-Waxman Act or similar foreign legislation. If we fail to receive such extensions or exclusive rights, our or our partners ability to prevent competitors from manufacturing, marketing and selling generic versions of our products will be materially impaired.

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

Our commercial success depends in part on our not infringing the patents and proprietary rights of third parties. Third parties may assert that we are employing their proprietary technology without authorization. In addition, third parties may obtain patents in the future and claim that use of our technologies infringes upon these patents.

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Furthermore, parties making claims against us may obtain injunctive or other equitable relief, which could effectively block our ability to develop and commercialize one or more of our products. Defense of these claims, regardless of their merit, would divert substantial financial and employee resources from our business. In the event of a successful claim of infringement against us, we may have to pay substantial damages, obtain one or more licenses from third parties or pay royalties. In addition, even in the absence of litigation, we may need to obtain additional licenses from third parties to advance our research or allow commercialization of our products. We may fail to obtain any of these licenses at a reasonable cost or on reasonable terms, if at all. In that event, we would be unable to develop and commercialize further one or more of our products.

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

As described elsewhere in these risk factors and in Part I, Item 3, *Legal Proceedings*, of this annual report on Form 10-K, we have initiated lawsuits to enforce our patent rights against certain generic pharmaceutical companies.

Risks related to our common stock

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

The realization of any of the risks described in these risk factors or other unforeseen risks could have a dramatic and adverse effect on the market price of our common stock. Between January 1, 2017 and December 31, 2017, the high and low sale prices of our common stock as reported on The Nasdaq Global Market varied between $11.90 and $18.99. Additionally, market prices for securities of biotechnology and pharmaceutical companies, including ours, have historically been very volatile. The market for these securities has from time to time experienced significant price and volume fluctuations for reasons that were unrelated to the operating performance of any one company.

The following factors, in addition to the other risk factors described in this section, may also have a significant impact on the market price of our common stock:

our or our partners level of success in commercializing our products;

our level of success in executing our commercialization strategies;