Risk Factors Comparison 2024-02-08 to 2023-02-09 Form: 10-K

Legend: **New Text** ~~Removed Text~~ Unchanged Text Moved Text Section

Risks Related to our Business and Industry • We are dependent on the commercial success of HETLIOZ ® ~~and ,~~ Fanapt **® and PONVORY** ®. • We face generic competition for HETLIOZ ®. • Future performance of HETLIOZ ® ~~and ,~~ Fanapt **®, and PONVORY** ® may be impacted by a number of factors including competing products or unanticipated safety issues. • We are subject to uncertainty relating to pricing and reimbursement policies in the U. S. • We have encountered third- party payors that refuse to cover or reimburse prescriptions written for HETLIOZ ®. • The FDA may not ~~accept~~ **approve** our tradipitant New Drug Application (NDA) **filing** ~~or~~ **for the use of tradipitant for patients with gastroparesis or accept our** supplemental New Drug Application (sNDA) ~~filings~~ **filing** for the use of tradipitant for ~~patients with gastroparesis and~~ patients with motion sickness, or the FDA may determine that our clinical trial results for tradipitant for these indications do not demonstrate adequate safety and substantial evidence of efficacy. • Global economic conditions may have an adverse effect on our business. • Global health crises and pandemics may adversely impact our business. • The FDA may not approve our **supplemental New Drug Applications (** sNDA **)** for HETLIOZ ® for the treatment of jet lag disorder or insomnia. • The FDA may not approve our sNDA for Fanapt ® for the treatment of bipolar I disorder. • We may be unable to enter into third- party collaborations to develop and commercialize our products, or collaborations we enter into with any such third party may not be commercially successful. • Even after we obtain regulatory approvals of a product, acceptance of the product in the marketplace is uncertain. • We **may not be able to successfully transition regulatory and supply responsibility for PONVORY ® from Janssen to us. • We** rely on, and will continue to rely on, outsourcing arrangements for many of our activities, including preclinical and clinical development and supply of HETLIOZ ®, HETLIOZ LQ ®, Fanapt **®, PONVORY** ® and our other products. • We may experience disruptions to our HETLIOZ ®, HETLIOZ LQ ® ~~or ,~~ Fanapt **® or PONVORY** ® supply chains. • We may fail to comply with government regulations regarding the sale and marketing of our products. • We may fail to comply with regulations and obligations related to the ongoing oversight of our products regarding, among other things, development, manufacturing, labeling, recordkeeping and reporting. • We may not market or distribute our products in a manner compliant with federal or state healthcare fraud and abuse laws. • 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. • Our revenues from Fanapt ® are substantially dependent on sales through a limited number of wholesalers. • We face substantial competition, which may result in others developing or commercializing products before or more successfully than we do. • FDA and foreign regulatory approval of our products is uncertain. • 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. • Clinical trials for our products are expensive and their outcomes are uncertain. • Our ability to use net operating loss carryforwards and tax credit carryforwards to offset future taxable income is dependent on generating future taxable income and may be limited, including as a result of transactions involving our common stock. • Our contract research organizations (CROs) may not successfully carry out their duties or we may lose our relationships with CROs. • We rely on a limited number of third- party manufacturers to formulate and manufacture our products and these manufacturers may not be able to satisfy our demand and alternative sources may not be available. • Materials necessary to manufacture our products may not be available on commercially reasonable terms, or at all. • We may lose key scientists or management personnel or fail to recruit additional highly skilled personnel. • We may be subject to product liability lawsuits. • European Union (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. • We may not be able to effectively market and sell our future products, if approved, in the U. S. • Healthcare legislative reform measures or developments arising from changes in political climate may have a material adverse effect on our business and results of operations. • We are subject to stringent laws, rules, regulations, policies, industry standards and contractual obligations regarding data privacy and security in foreign jurisdictions which are subject to change and reinterpretation. 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 efforts to protect the proprietary nature of the intellectual property related to our products may not be adequate. • We are, 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. • We may not be able to obtain protection under the Hatch-Waxman Act and similar foreign legislation to extend our patents and to obtain market exclusivity for our products. • Generic competitors have obtained FDA approval of generic versions of HETLIOZ ® in the U. S. • We may not be successful in the development of products for our own account. • 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. ITEM 1. BUSINESS Overview Vanda Pharmaceuticals Inc. (we, our, the Company or Vanda) is a leading global biopharmaceutical company focused on the development and commercialization of innovative therapies to address high unmet medical needs and improve the lives of patients. We strive to advance novel approaches to bring important new medicines to market through responsible innovation. We are committed to the use of technologies that support sound science, including genetics and genomics, in drug discovery, clinical trials and the commercial positioning of our products. Our commercial portfolio is currently comprised of ~~two~~ **three** products, HETLIOZ ® for the treatment of Non- 24- Hour Sleep- Wake Disorder (Non- 24) and **for the treatment of** nighttime sleep disturbances in Smith- Magenis Syndrome (SMS) ~~and ,~~ Fanapt ® for the treatment of schizophrenia **and**

PONVORY ®, which we acquired the U. S. and Canadian rights to on December 7, 2023, for the treatment of relapsing forms of multiple sclerosis (MS), to include clinically isolated syndrome, relapsing- remitting disease and active secondary progressive disease, in adults . HETLIOZ ® is the first product approved by the FDA for patients with Non- 24 and **for** patients with SMS. In addition, we have a number of drugs in development, including: • HETLIOZ ® (tasimelteon) for the treatment of jet lag disorder, insomnia, delayed sleep phase disorder (DSPD ~~), sleep disturbances in autism spectrum disorder (ASD~~) and pediatric Non- 24; • Fanapt ® (iloperidone) for the treatment of bipolar I disorder and ~~Parkinson' s disease psychosis and~~ a long acting injectable (LAI) formulation for the treatment of schizophrenia **; • PONVORY (ponesimod) for the treatment of inflammatory / autoimmune disorders, including but not limited to ulcerative colitis, psoriasis, Crohn' s disease, atopic dermatitis, eosinophilic esophagitis and alopecia areata** ; • Tradipitant (VLY- 686), a small molecule neurokinin- 1 (NK- 1) receptor antagonist, for the treatment of gastroparesis, motion sickness ~~,~~ **and** atopic dermatitis ~~, and COVID- 19 pneumonia~~ ; • ~~VTR-~~ **VHX** ~~- 297~~ **896** , ~~a small molecule histone deacetylase (HDAC) inhibitor for~~ the ~~treatment~~ **active metabolite** of **iloperidone** ~~hematologic malignancies and with potential use as a treatment for several oncology indications~~ ; • Portfolio of Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) activators and inhibitors, including VSJ- 110 for the treatment of dry eye and ocular inflammation and VPO- 227 for the treatment of secretory diarrhea disorders, including cholera; • **VTR- 297, a small molecule histone deacetylase (HDAC) inhibitor for the treatment of onychomycosis, hematologic malignancies and with potential use as a treatment for several oncology indications; •** VQW- 765, a small molecule nicotinic acetylcholine receptor partial agonist, for the treatment of **social /** performance anxiety and psychiatric disorders ~~; • VHX- 896, the active metabolite of iloperidone~~ ; and • Antisense oligonucleotide (ASO) molecules **, including VCA- 894A for the treatment of Charcot- Marie- Tooth Disease, Type 2S (CMT2S), caused by cryptic slice site variants within IGHMBP2** . We were incorporated in 2002 and commenced operations in 2003. We are headquartered in Washington, D. C. Our Strategy Our goal is to further solidify our position as 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 **® and PONVORY** ®; • Enter into strategic partnerships to supplement our capabilities and to extend our commercial reach; • Pursue the clinical development and regulatory approval of our products, including tradipitant; • Apply our pharmacogenetics and pharmacogenomics expertise to differentiate our products; • Expand our product portfolio through the identification and acquisition of additional products; and • Utilize novel and innovative approaches in pursuit of each of these strategies. Commercialized Products Our commercial product portfolio consists of: Product Indication ~~2022~~ **2023** Net Sales (in millions) Geography Non- 24 (capsules) Nighttime sleep disturbances in SMS (capsules and HETLIOZ LQ ® oral suspension) $ ~~159~~ **100** . ~~7~~ **2** United StatesEurope (Non- 24 in blind patients only) Schizophrenia (tablets) $ ~~94~~ **90** . ~~7~~ **9** United StatesIsrael **Relapsing forms of multiple sclerosis (tablets) $ 1. 6 United StatesCanada** HETLIOZ ® for Non- 24 (capsules) In January 2014, HETLIOZ ® capsules were approved in the U. S. for the treatment of adults with Non- 24. Non- 24 is a serious, rare and chronic circadian rhythm sleep- wake 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. 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. HETLIOZ ® was launched commercially in the U. S. in April 2014. In addition, 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 included post- marketing commitments related to a pediatric investigation plan. This authorization was renewed in July 2020 for an unlimited duration ~~,~~ and is valid in the 27 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. Non- 24 also can affect sighted individuals. As with the totally blind, Non- 24 in sighted individuals appears to be a comorbidity with certain other conditions. For example, a comorbidity has been established between psychiatric mood disorders and Non- 24. Hospitalized individuals with neurological and psychiatric disorders can become insensitive to social cues, which may predispose them to the development of Non- 24. This recognition of comorbidity led ~~Vanda~~ **us** to an initiative to engage with the psychiatric community. Patients diagnosed with traumatic brain injury, including concussions, frequently suffer from sleep disorders, some of which may be circadian rhythm sleep- wake disorders, including Non- 24. While there are no EC approved treatments for Non- 24 other than HETLIOZ ®, and only recently

has the FDA approved generics for the treatment of Non- 24, 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. HETLIOZ ® for SMS (capsules and oral suspension) In December 2020, HETLIOZ ® capsules and oral suspension (HETLIOZ LQ ®) were approved in the U. S. for the treatment of adults and children, respectively, with nighttime sleep disturbances in SMS. HETLIOZ ® capsules, for adults with SMS, were immediately available after approval and the HETLIOZ LQ ® liquid formulation, for children with SMS, became available in the first quarter of 2021. SMS is a developmental disorder that is caused by a small deletion of human chromosome 17p. In more rare cases, SMS is caused by a point mutation in the RAI1 gene, which resides in the deleted region. HETLIOZ ® is the first FDA-approved medication for patients with SMS. In April 2010, the FDA granted orphan drug designation status for HETLIOZ ® in the treatment of sleep disorder in SMS. SMS is estimated to affect 1 / 15, 000- 25, 000 births in the U. S. SMS is not usually inherited but rather is caused by a de- novo deletion. Patients with SMS present with a number of physical, mental and behavioral problems. The most common symptom of SMS is a severe sleep disorder associated with significant disruption in the lives of patients and their families **. In September 2023, the EMA designated HETLIOZ ® as an orphan medicinal product for the treatment of SMS** . While there are no FDA approved treatments for patients with SMS other than HETLIOZ ®, there are a number of drugs approved and prescribed for patients with sleep disorders that may be used to treat patients with SMS. The most commonly prescribed drugs are hypnotics. See Competition below for a discussion of commonly prescribed drugs for patients with sleep disorders. Fanapt ® for schizophrenia (tablets) Fanapt ® is a product approved 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. At that time, we had certain worldwide exclusive rights relating to Fanapt ®, which we obtained pursuant to a sublicense agreement entered into with Novartis Pharma AG (Novartis) in June 2004. In October 2009, we amended and restated our sublicense agreement with Novartis pursuant to which Novartis retained 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 us as part of a settlement agreement. Additionally, our distribution partners launched Fanapt ® in Israel in 2014. In May 2016, the FDA approved a supplemental New Drug Application (sNDA) for Fanapt ® for the maintenance treatment of schizophrenia in adults. 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 ®. **PONVORY ® for relapsing multiple sclerosis (tablets) PONVORY ® is a product approved for the treatment of relapsing forms of MS (RMS), to include clinically isolated syndrome, relapsing- remitting disease and active secondary progressive disease, in adults. In December 2023, we purchased the right to market and sell PONVORY ® in the U. S. and Canadian markets from Actelion Pharmaceuticals Ltd. (Janssen), a Johnson & Johnson Company. In March 2021, the FDA granted U. S. marketing approval of PONVORY ® for the treatment of RMS in adults. Health Canada approved PONVORY ® for the treatment of RMS in April 2021. MS is a chronic autoimmune inflammatory disease of the central nervous system (CNS) in which immune cells attack myelin (the protective casing that insulates nerve cells), damaging or destroying it and causing inflammation. This affects how the CNS processes information and communicates with the rest of the body, causing the neurologic signs and symptoms of MS. Symptoms vary by person, but common symptoms include fatigue, balance and walking problems, numbness or tingling, dizziness and vertigo, vision problems, bladder and bowel problems and weakness. PONVORY ® was launched commercially in the U. S. in April 2021 and in Canada in November 2021 by one of the Johnson & Johnson Companies. There are a number of drugs approved and prescribed to treat patients with MS. See Competition below for a discussion of these commonly prescribed drugs.** 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. Our product pipeline currently consists of the following products in clinical development or under regulatory review: HETLIOZ ® for jet lag disorder In March and May 2018, respectively, we announced the results of our JET8 and JET studies for the treatment of jet lag disorder. In the JET8 clinical study, HETLIOZ ® demonstrated significant and clinically meaningful benefits in nighttime and daytime symptoms of jet lag disorder, including improvement in sleep time and benefits in measurements of next day alertness. The JET study showed effectiveness in treating travelers who traveled either five or eight time zones from Washington, ~~DC~~ **D. C.** to London and San Francisco or Los Angeles to London, respectively. The results support the previously reported pivotal JET5 and JET8 Phase III studies, which demonstrated improvements in patients who experienced circadian advances of five and eight hours, respectively. Additionally,

in September 2018, we announced results from a driving study, which demonstrated that tasimelteon did not impair measures of driving performance. The FDA accepted the filing of our sNDA for HETLIOZ ® for the treatment of jet lag disorder in December 2018. The FDA determined the action target **action** date under the Prescription Drug User Fee Act Amendments of 2017 to be August 16, 2019 and, on that date, we received a complete response letter (CRL) from the FDA. The FDA asserted in the CRL that the measures demonstrating improved sleep were of unclear clinical significance. We met with the FDA to discuss the CRL in a Post Action meeting and in 2022 we requested the opportunity for a hearing with the FDA on the approvability of the jet lag disorder sNDA. We filed a lawsuit against the FDA in September 2022 demanding that the FDA immediately publish in the Federal Register a notice of opportunity for a hearing on the jet lag disorder sNDA. The FDA then published the notice in the Federal Register in October 2022. We ~~are undergoing discussions~~ **have asked the U. S. District Court for the District of Columbia (DC District Court) to, among other things, compel the FDA to comply** with **its obligations and declare that its lack of compliance violates the FDCA and** the FDA **regulations. In January 2024, the DC District Court held an oral argument** on **dispositive cross- motions, following which** the ~~timing of such~~ **DC District Court granted our motion for summary judgment. The DC District Court ruled that the FDA violated the statute and ordered the FDA to either finally resolve our application or commence a** hearing **on or before March 5, 2024. Our lawsuit remains pending. We have asked the DC District Court to, among other things, compel the FDA to comply with its obligations and declare that its lack of compliance violates the FDCA and the FDA regulations. In January 2024, the DC District Court held an oral argument on dispositive cross- motions, following which the DC District Court granted our motion for summary judgment. The DC District Court ruled that the FDA violated the statute and ordered the FDA to either finally resolve our application or commence a hearing on or before March 5, 2024. Our lawsuit remains pending**. Jet lag disorder is a common circadian disorder frequently observed in millions of travelers who cross multiple time zones. Jet lag disorder is characterized by nighttime sleep disruption, a decrease in daytime alertness and impairment to social and occupational functioning. Jet lag disorder symptoms are more severe during eastward travel. U. S. Department of Commerce, International Trade Administration reports state that more than 20 million U. S. residents make trips abroad each year to overseas destinations in Europe, the Middle East and Asia. HETLIOZ ® for insomnia HETLIOZ ® is effective in improving sleep onset difficulty in people with primary insomnia with the effect observed as early as the first night of treatment. A Phase III, multi- center, placebo- controlled, 4- week trial evaluated patients with chronic primary insomnia. Two transient insomnia studies induced by phase advance of the sleep- wake cycle were also conducted with five- hour and eight- hour phase advance, which showed a significant effect the first night in improving sleep parameters. **In July 2023, the FDA accepted our sNDA for HETLIOZ ® in insomnia for filing and set a target action date of March 4, 2024 under the Prescription Drug User Fee Act (PDUFA) for its decision.** HETLIOZ ® for pediatric Non- 24 We plan to develop HETLIOZ ® for the treatment of pediatric Non- 24. A pharmacokinetic study of the HETLIOZ ® pediatric liquid formulation was completed in the first quarter of 2018. HETLIOZ ® for DSPD A Phase III study of HETLIOZ ® in DSPD is ongoing. DSPD is a circadian rhythm disorder in which a person' s sleep is delayed beyond the socially acceptable or conventional bedtime. This delay in falling asleep causes difficulty in waking up at the desired time and affects social and occupational functioning. DSPD is likely the most prevalent circadian- rhythm sleep disorder, affecting approximately 1 % of the population, and there is no FDA approved treatment at this time ~~. HETLIOZ ® for ASD A clinical program of HETLIOZ ® for the treatment of symptoms of ASD is ongoing. Sleep disturbances in ASD are a high unmet medical need in people with ASD and have been characterized in the literature to include difficulties falling and staying asleep~~. Fanapt ® for bipolar I disorder In December 2022, we announced Fanapt ® was effective in the treatment of acute manic and mixed episodes associated with bipolar I disorder in adults in a randomized double- blind placebo controlled Phase III study. The primary endpoint measured in Week 4 of treatment was assessed by the Young Mania Rating Scale (YMRS), a rating scale of clinical severity in the core symptoms of mania. At the end of the 4- week study, Fanapt ® treated patients showed a larger improvement than placebo treated patients, and this difference was highly statistically significant. Statistically significant benefit in the Fanapt ® group over placebo was observed as early as the Week 2 assessment. Consistent with the total YMRS score, the individual YMRS subscale items also showed improvement in the Fanapt ® group versus the placebo group over the course of the 4- week study. Other outcomes, such as Clinician Global Impression of Severity (CGI- S) and Clinician Global Impression of Change (CGI- C), also achieved statistical significance. Bipolar disorders are brain disorders that cause changes in a person' s mood, energy and ability to function. Bipolar disorder is a category that includes three different conditions- bipolar I, bipolar II and cyclothymic disorder. People with bipolar disorders have extreme and intense emotional states that occur at distinct times, called mood episodes. These mood episodes are categorized as manic, hypomanic or depressive. People with bipolar disorders generally have periods of normal mood as well. **In August 2023, the FDA accepted our sNDA for Fanapt ® in bipolar I disorder in adults for filing and set a PDUFA target action date of April 2, 2024 for its decision.** Fanapt ® for schizophrenia (LAI) In October 2018, we enrolled our first patient in a pharmacokinetic study of the LAI formulation of Fanapt ®. This pharmacokinetic study is ongoing and will serve to inform the dosing for a later clinical study of Fanapt ® LAI for the treatment of schizophrenia. ~~Fanapt~~ **The mechanism of action of PONVORY ® makes it also a potential therapeutic candidate** for ~~Parkinson~~ **the treatment of a diverse group of inflammatory / autoimmune disorders including but not limited to ulcerative colitis, psoriasis, Crohn** ' s disease ~~psychosis A~~ **, atopic dermatitis, eosinophilic esophagitis and alopecia areata. In a randomized placebo controlled** clinical ~~program of Fanapt~~ **study, PONVORY ® has been shown to reduce** ~~in Parkinson' s disease psychosis is ongoing. Parkinson' s disease is a neurodegenerative disorder that affects predominately dopaminergic neurons in a specific area of~~ the **symptoms** ~~brain called substantia nigra. There are approximately one million adults in the U. S. with Parkinson' s disease. Between 20 %~~ and **signs** ~~40 %~~ of **psoriasis** ~~persons with Parkinson' s disease experience a combination of hallucinations and delusions. The disease is associated with significant caregiver burden~~. Tradipitant for gastroparesis In December 2018, we announced results from a Phase II randomized clinical study (2301) of tradipitant as a monotherapy in the treatment of gastroparesis. Several symptom severity scales were used to assess gastroparesis

symptoms, including the Gastroparesis Symptom Index (GCSI), Patients Assessment of Upper Gastrointestinal Disorders- Symptoms (PAGI- SYM), and Patient Global Impression of Change (PGI- C) as well as a Clinician Global Impression of Severity (CGI- S). Tradipitant met the primary endpoint of the study of change in nausea score as measured by patient daily diaries and also met the related endpoint of improvement in the number of nausea free days. Tradipitant also showed significant improvement in most of the secondary endpoints studied, including several key scales reflecting overall gastroparesis symptoms, specifically GCSI, PAGI- SYM, CGI- S, and PGI- C. In February 2022, we announced results from our Phase III clinical study, VP- VLY- 686- 3301, evaluating the efficacy and safety of tradipitant in treating the symptoms of gastroparesis. The study did not meet its prespecified primary endpoint, which was the difference between drug and placebo on the change of the severity of nausea from baseline at week 12 of treatment. Both treatment arms showed significant improvements from baseline on nausea as well as the other core symptoms of gastroparesis. When restricting the analysis in the group of patients that used no rescue medications at baseline and adjusting for poor compliance, we identified strong evidence of a drug effect across a number of symptoms and across the duration of the study, including a significant and meaningful effect at the prespecified primary endpoint of nausea change at week 12. The FDA may not view this data as constituting substantial evidence of efficacy for tradipitant in any indication for the treatment of gastroparesis or its symptoms, for any length of treatment. ~~We are preparing for submission~~ **The open- label phase** of **the study remains open** ~~an NDA for tradipitant for patients with gastroparesis~~. We believe that tradipitant has a well- established safety profile, as demonstrated by the results of extensive testing in animals and humans. Despite these results, however, the FDA informed us in December 2018 that in order to treat patients beyond 12 weeks, we ~~will~~ **would** have to conduct a nine- month non- rodent chronic toxicity study. This currently limits our ability to collect safety data in humans for more than 12 weeks. The non- rodent study required by the FDA necessitates the sacrifice of dozens of animals and we have disputed the necessity of a nine- month non- rodent chronic toxicity study. In February 2019, we filed a lawsuit in the U. S. District Court for the District of Columbia (DC District Court) challenging the FDA' s position, but we ultimately did not prevail. Despite our disagreement with the FDA, the preclinical package has allowed us to continue to conduct all of the efficacy studies necessary for New Drug Application (NDA) filing. Moreover, in July 2020, the FDA authorized tradipitant through an expanded access program (EAP) for a single patient. An EAP allows a patient to request the use of tradipitant, prior to NDA approval, for up to six months with an option to request renewal. Since then, certain patients who experienced a benefit in tradipitant studies have requested and received expanded access, while others have been denied treatment under the EAP. The EAP is ongoing and a number of patients have initiated treatment. Although this EAP is not intended for data collection, we collect safety data from this cohort of expanded access patients and ~~plan to include~~ **included** this data in the NDA **that we submitted** for tradipitant for patients with gastroparesis **. In December 2023, the FDA accepted our NDA for tradipitant in gastroparesis for filing and set a PDUFA target action date of September 18, 2024. If approved, tradipitant will be the first novel drug to be approved by the FDA for the treatment of gastroparesis in over 40 years and tradipitant is the first novel drug to be accepted for review by the FDA for gastroparesis in over 30 years** . The FDA may disregard such safety data when reviewing the NDA. The lack of long- term (i. e., more than 12 weeks in humans) safety data would likely impact the FDA' s willingness to approve tradipitant for a chronic indication. However, because long-term safety data is not normally a requirement for short- term indications, and with a preclinical profile that has not precluded clinical development, we believe the package ~~is~~ **was** complete for any NDA filing to treat patients for 12 weeks or less. For example, the FDA has communicated to us that it is considering an indication for the short- term relief of nausea in gastroparesis. While this short- term indication is not preferred, we would consider accepting this limited indication while continuing to pursue a chronic indication. However, the FDA may not deem the safety information sufficient even for a short-term indication. Moreover, FDA authorization of an EAP is not a guarantee of or a step in obtaining full FDA approval of an NDA. Gastroparesis is a serious medical condition characterized by delayed gastric emptying associated with the symptoms of nausea, vomiting, bloating, fullness after meals and abdominal pain, along with significant impairment of social and occupational functioning. A paper by Rey et al published in the January 2012 Journal of Neurogastroenterology and Motility estimated the prevalence of gastroparesis in the U. S. to be approximately six million patients, many of whom remain undiagnosed. Tradipitant for motion sickness In July 2019, we reported tradipitant was effective in treating motion sickness in a randomized double blind placebo controlled Phase II clinical study conducted in the Pacific Ocean. The study had two primary endpoints: percentage of participants vomiting, and Motion Sickness Severity Scale (MSSS) Worst score. In the overall population, a significantly higher percentage of participants experienced vomiting in the placebo arm as compared to the tradipitant arm. The MSSS Worst score endpoint also favored tradipitant, but the difference did not reach statistical significance. The protocol for a pivotal Phase III motion sickness study was discussed with the FDA at the end of Phase II meeting, and the FDA agreed with the adequacy of the program design to support an NDA. ~~The~~ **In May 2023, we announced positive results from the first** Phase III study **of tradipitant in motion sickness, confirming the previously reported results demonstrating that tradipitant is effective in the prevention of vomiting associated with motion sickness. A second Phase III study of tradipitant in motion sickness** is ongoing. Motion sickness is a disorder that arises often as a response to real or perceived movement, as occurring during vehicular travel. Vomiting is the most disturbing symptom of motion sickness, although the disorder is often accompanied by a constellation of symptoms that includes nausea, sweating, pallor, headache and anorexia. Motion sickness is one of the most prevalent episodic disorders in the world, whose prevalence has dramatically increased with world population mobility over the last 100 years. It is reported that approximately 30 % of the general population suffers from motion sickness under ordinary travel conditions that include sea, air and land travel. Tradipitant for atopic dermatitis We announced results in September 2017 from a randomized Phase II clinical study of tradipitant as a monotherapy in the treatment of patients with atopic dermatitis. Tradipitant was shown to improve the intensity of the worst itch patients experienced, as well as atopic dermatitis disease severity. On the pre- specified primary endpoint of Average Itch Visual Analog Scale (VAS), tradipitant showed improvement over placebo, but this improvement was not significant due to high placebo effect and the lack

of sensitivity of this measure. In June 2018, we initiated EPIONE, a Phase III study of tradipitant for pruritus in atopic dermatitis. In October 2019, we began enrolling patients in EPIONE 2, a second Phase III clinical study of tradipitant in atopic dermatitis. We announced results of EPIONE in February 2020. The EPIONE study did not meet its primary endpoint in reduction of pruritus across the overall study population. However, the antipruritic effect of tradipitant was robust in the mild atopic dermatitis population. The EPIONE study continued to demonstrate that tradipitant is safe and well- tolerated. The EPIONE 2 study was placed on hold in 2020. Atopic dermatitis is a chronic, relapsing inflammatory skin disorder characterized by the symptom of intense and persistent pruritus or itch. Other clinical features include erythema, excoriation, edema, lichenification, oozing and xerosis. Atopic dermatitis is a common skin disorder affecting millions of people worldwide. Currently, there are very few safe systemic treatments available for atopic dermatitis, representing a significant unmet medical need in this population. A 2015 Decision Resources Group report estimated that 9. 8 million individuals were diagnosed with atopic dermatitis in the U. S., of which approximately 6. 4 million were drug- treated atopic dermatitis patients. ~~Tradipitant for COVID~~ **In 2021, we initiated a bioequivalence study of Fanapt ® and VHX** - **896** ~~19 pneumonia In April 2020~~ , ~~we announced~~ the ~~initiation~~ **active metabolite** of ~~a~~ **iloperidone. We believe that VHX- 896** ~~Phase~~ -- **has** ~~III~~ **the potential to improve the** clinical ~~study~~ **profile of Fanapt ® and create sustained** , **long** ~~ODYSSEY VLY~~ - **term value** ~~686- 3501,~~ in ~~hospitalized patients with COVID- 19. We received permission from the FDA to proceed with the study for~~ the treatment ~~and prevention~~ of **psychiatric disorders** ~~pneumonia associated with COVID- 19. Enrollment in the VLY- 686- 3501 study closed in August 2021 because the study met the pre- defined futility criteria, indicating that the study was unlikely to succeed in its pre- specified primary endpoint. The study was designed to determine whether tradipitant plus standard of care is superior to placebo plus standard of care in treating hospitalized patients with COVID- 19 pneumonia who required supplemental oxygen support. An independent data and safety monitoring board (DSMB) met to assess the planned interim analysis results and determined that the study is unlikely to show a significant difference between treatment arms at the pre- specified primary endpoint and recommended termination of the study for futility. The DSMB also determined that there are no safety concerns that contributed to its recommendation. We have continued the genetics component of the study with the goal of identifying genetic susceptibility factors contributing to the incidence of severe pneumonia among patients infected with COVID- 19. COVID- 19 is associated with a lower respiratory tract inflammation that often progresses to acute respiratory distress syndrome requiring mechanical ventilation. Tradipitant targets the neurokinin- 1 receptor, which is coded by the TACR1 gene and is the main receptor for substance P, an 11 amino acid neuropeptide with a diverse set of functions. It has been shown that the substance P NK- 1 receptor system is involved in the neuroinflammatory processes that leads to significant lung injury following a number of insults~~ , including ~~viral challenges~~ **schizophrenia and bipolar I disorder** . **Other products** In the fourth quarter of 2018, we initiated a clinical study in patients with hematologic malignancies. Enrollment in the Phase I / II clinical study (1101) of VTR- 297 in hematologic malignancies is ongoing. VTR- 297 is a small molecule HDAC inhibitor with potential use as a treatment for several oncology indications. **In January 2024, the FDA approved our Investigational New Drug (IND) application to evaluate VTR- 297 for the treatment of onychomycosis.** Portfolio of CFTR activators and inhibitors A clinical program in VSJ- 110 is ongoing. We are evaluating VSJ- 110 for the treatment of allergic conjunctivitis. VSJ- 110 is a small molecule nanomolar potency CFTR activator. VSJ- 110 has shown efficacy in a dry eye model and exhibited anti- inflammatory properties in both in vitro and in vivo assays. In addition, an early stage CFTR inhibitor program is planned for VPO- 227 for the treatment of secretory diarrhea disorders, including cholera. We believe that VPO- 227 has the potential to be an orally administered treatment for cholera. In October 2022, VPO- 227 was granted orphan drug designation by **the** FDA for the treatment of cholera. We are evaluating VQW- 765 for the treatment of psychiatric disorders. In December 2022, we announced results from our Phase II study, VP- VQW- 765- 2201 (Study 2201), of a single- dose treatment to alleviate acute performance anxiety in social situations. In the clinical study, 230 volunteers with prior history of performance anxiety were randomized to receive a single dose of VQW- 765 or placebo and were challenged with the standardized Trier Social Stress Test (TSST). The TSST creates an acute stress by requiring participants to make an interview- style presentation in front of a panel who provides no feedback or encouragement. Participants who received VQW- 765 showed numerically lower stress levels compared to those who received placebo. A significant relationship was also seen between exposure to VQW- 765 (amount of drug measured in blood) and the clinical response. 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. ~~Other products In 2021, we initiated a bioequivalence study of Fanapt ® and VHX- 896, the active metabolite of iloperidone. We believe that VHX- 896 has the potential to improve the clinical profile of Fanapt ® and create sustained, long- term value in the treatment of psychiatric disorders.~~ ASO Molecules In 2022, we announced a research and development collaboration agreement with OliPass Corporation (OliPass) to jointly develop a set of ASO molecules based on OliPass' proprietary modified peptide nucleic acids. The collaboration focuses on editing and modifying gene expression using ASOs in disease states where the expression of genes is either altered or the sequence of the expressed genes can be altered for therapeutic benefit. OliPass' unique OliPass Peptide Nucleic Acids technology provides the delivery platform to enable these gene expression modifications **. ASOs may have broad applicability in addressing a number of disorders, from nervous system treatments to systemic treatments. In June 2023, VCA- 894A, an ASO molecule, was granted orphan designation by FDA for the treatment of a patient with CMT2S, caused by cryptic splice site variants within IGHMBP2. In January 2024, we announced that the FDA had approved the Investigational New Drug (IND) application to evaluate VCA- 894A for the treatment of a patient with CMT2S. CMT2S is a rare subtype of Charcot- Marie- Tooth disease (CMT), an inherited peripheral neuropathy for which there is no available treatment. The estimated prevalence of CMT is 1 in 2, 500 individuals, with varying clinical features dependent on the various genetic variants of CMT. The prevalence of CMT2S is estimated to be less than 1 in 1, 000, 000 worldwide** . For more detailed information regarding our clinical trial results and regulatory activities for our products please refer to our SEC filings and press releases, which can be found on the SEC EDGAR website and on our website www.

vandapharma. com. Information contained on those websites is not incorporated by reference into this Annual Report or any other report or document that we file with the SEC. License Agreements Our rights to develop and commercialize **certain of** our products are subject to the terms and conditions of licenses granted to us by other pharmaceutical companies. 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 ®. We have paid BMS $ 37. 5 million in upfront fees and milestone obligations. We have no remaining milestone obligations to BMS. Additionally, we are obligated to make royalty payments on HETLIOZ ® net sales to BMS. The royalty period in each territory where we commercialize HETLIOZ ® is 10 years following the first commercial sale in the territory. In territories outside the U. S., the royalty is 5 % on net sales. In December 2022, the royalty on net sales in the U. S. decreased from 10 % to 5 %. This U. S. royalty will end in April 2024. 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 are obligated to use 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. 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 paid directly to Sanofi S. A. (Sanofi) a fixed royalty of 3 % of net sales through December 2019 related to manufacturing know- how. No further royalties on manufacturing know- how are payable by us. We are also obligated to pay Sanofi a fixed royalty on Fanapt ® net sales equal up to 6 % on Sanofi know- how not related to manufacturing under certain conditions for a period of up to 10 years in markets where the NCE patent has expired or was not issued. We are obligated to pay this 6 % royalty on net sales in the U. S. through November 2026. No further royalties on know- how not related to manufacturing will be payable by us for net sales in the U. S. after November 2026. 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. In April 2012, we entered into a license agreement with Eli Lilly and Company (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- 1 receptor antagonist, tradipitant, for all human indications. Lilly is eligible to receive future payments based upon achievement of specified development, regulatory approval and commercialization milestones as well as tiered- royalties on net sales at percentage rates up to the low double digits. We have paid Lilly $ ~~3~~ **5** . 0 million in upfront fees and development milestones ~~. As of December 31~~ , ~~2022, remaining milestones include~~ **including** a $ 2. 0 million development milestone ~~due upon~~ **paid in December 2023 for** the filing of the first marketing authorization for tradipitant in ~~either~~ the U. S. or the E. U **. As of December 31** , **2023, remaining milestones include** $ 10. 0 million and $ 5. 0 million **milestones** for the first approval of a marketing authorization for tradipitant in the U. S. and **the** E. U., respectively, and up to $ 80. 0 million for sales milestones. 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. 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. UCSF is eligible to receive future payments based upon achievement of specified development, regulatory approval and commercialization milestones as well as single- digit tiered- royalties on net sales. We have paid UCSF $ 1. 6 million in upfront fees and development milestones. As of December 31, ~~2022~~ **2023** , remaining milestones include $ 11. 9 million for development milestones and $ 33. 0 million for future regulatory approval and sales milestones. Included in the $ 11. 9 million in development milestones are $ 1. 1 million of milestone obligations due upon the conclusion of clinical studies for each licensed product, not to exceed $ 3. 2 million in total for the CFTR portfolio. 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 us of our obligation to pay royalties or other payments owed, if any, to UCSF under the terms of the agreement. 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. Patents and Proprietary Rights; Hatch- Waxman Protection Our products are protected from unauthorized use by others only to the extent that our products are covered

through regulatory protections or by valid and enforceable patents, either licensed to us by others or generated through our activities internally, that give us sufficient proprietary rights. Accordingly, securing patents, regulatory data package protection, and other proprietary rights ~~is~~ **are** an essential element of our business strategies. **PONVORY ®,** ~~Tradipitant~~ **tradipitant** and VQW- 765 are covered by NCE and other patents and patent applications related to their respective medicinal uses. In addition, NCE patent protection has been sought for VTR- 297 and CFTR. Patent applications for these active ingredients remain pending. Although the NCE patents protecting Fanapt ® and HETLIOZ ® have expired, Fanapt ® remains protected by additional patents and HETLIOZ ® remains protected by additional patents, some of which we have asserted against current generic competitors. For more on the license and sublicense arrangements related to these active ingredients, see License Agreements above. For more on patent litigation, see Note ~~16~~ **17** , Legal Matters, to the consolidated financial statements in Part II, Item 8 of this Annual Report and the risk factor entitled " We are, 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, " in Part I, Item 1A of this Annual Report, each of which is incorporated herein by reference. In addition, we have filed for patents based on our own discoveries that seek to provide additional protection for HETLIOZ ® and Fanapt ®. A comprehensive list of active patents for our U. S. commercial products is available in the Approved Drug Products with Therapeutic Equivalence Evaluations (Orange Book) for our commercial products and is also provided in the table below. Members of these patent families are also issued or pending in a number of territories, such as Europe and Japan. The patents in the table below that are marked with " * " are the subject of ongoing patent litigation. See Note ~~16~~ **17** , Legal Matters, to the consolidated financial statements in Part II, Item 8 of this Annual Report and the risk factor entitled " We are, 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, " in Part I, Item 1A of this Annual Report, each of which is incorporated herein by reference, for additional information. ProductNumber TypeHETLIOZ ® US 9, 060, 995 Method of treatmentUS 9, 539, 234 Method of treatmentUS 9, 549, 913 Method of treatmentUS 9, 730, 910 * Method of treatmentUS 9, 855, 241 Method of treatment US RE46604 * Method of treatmentUS 10, 071, 977Drug substanceUS 10, 149, 829 * Method of treatmentUS 10, 179, 119Method of treatmentUS 10, 376, 487 * Method of treatmentUS 10, 449, 176Method of treatmentUS 10, 610, 510Method of treatmentUS 10, 610, 511Method of treatmentUS 10, 829, 465Drug substanceUS 10, 945, 988Method of treatmentUS 10, 980, 770Method of treatmentUS 11, 141, 400Method of treatmentUS 11, 266, 622Method of treatmentUS 11, 285, 129 * Method of **treatmentUS 11, 566, 011Drug substanceUS 11, 633, 377Method of treatmentUS 11, 759, 446Method of treatmentUS 11, 760, 740Drug substanceUS 11, 786, 502Method of treatmentUS 11, 833, 130Method of treatmentUS 11, 850, 229Method of** treatmentHETLIOZ LQ ® US 9, 539, 234Method of treatmentUS 9, 730, 910 * Method of treatmentUS 10, 071, 977Drug ~~substanceUS~~ -- **substance ProductNumber TypeUS** 10, 149, 829 * Method of treatmentUS 10, 179, 119Method of treatmentUS 10, 376, 487 * Method of treatmentUS 10, 610, 510Method of treatmentUS 10, 610, 511Method of treatmentUS 10, 829, 465Drug substanceUS 10, 980, 770Method of treatmentUS 11, 141, 400Method of treatmentUS 11, 202, 770Drug formulationUS 11, 266, 622Method of treatmentUS 11, 285, 129 * Method **of treatmentUS 11, 566, 011Drug substanceUS 11, 633, 377Method of treatmentUS 11, 759, 446Method of treatmentUS 11, 760, 740Drug substanceUS 11, 786, 502Method of treatmentUS 11, 833, 130Method of treatmentUS 11, 850, 229Method** of treatmentFanapt ® US 8, 586, 610 * Method of treatmentUS 8, 652, 776 Method of treatmentUS 8, 999, 638 Method of treatmentUS 9, 072, 742 Method of treatmentUS 9, 074, 254 Method of treatmentUS 9, 074, 255 Method of treatmentUS 9, 074, 256 Method of treatmentUS 9, 138, 432 * Method of treatmentUS 9, 157, 121 Method of **treatmentPONVORY ® US 8, 273, 779Method of** ~~treatment~~ **treatmentUS 9, 000, 018Method of treatmentUS 9, 062, 014Drug substanceUS 10, 220, 023Method of treatmentUS RE43728Drug substance** HETLIOZ ® and HETLOZ LQ ® Our rights to the NCE patent covering HETLIOZ ® capsules and oral suspension (HETLIOZ LQ ®) and related intellectual property have been acquired through a license with BMS. HETLIOZ ® and its formulations, genetic markers and uses are the subject of numerous patent filings for which protection has been sought in selected countries worldwide. The NCE patent covering HETLIOZ ® expired in December 2022 in the U. S., which is inclusive of a five- year extension granted under the Hatch- Waxman Act in October 2018. Corresponding NCE patent protection has expired in most other markets. The U. S. Patent and Trademark Office has issued ~~17~~ **22** method of treatment patents for HETLIOZ ® that will expire between 2033 and ~~2035~~ **2041** and ~~three~~ **four** drug substance patents that will expire in 2035. Additionally, the U. S. Patent and Trademark Office has issued a drug formulation patent for HETLIOZ LQ ® that will expire in 2040. We also have other pending patent applications covering methods of treatment and compositions of tasimelteon (HETLIOZ ® active ingredient) oral suspensions. We filed several Hatch- Waxman lawsuits in the U. S. District Court for the District of Delaware (Delaware District Court) against Teva Pharmaceuticals USA, Inc. (Teva), Apotex Inc. (Apotex), MSN Pharmaceuticals, Inc. and MSN Laboratories Private Limited (MSN) (collectively, the HETLIOZ ® Defendants) asserting infringement of patents covering HETLIOZ ® 20 mg capsules. In January 2022, we entered into a license agreement with MSN and Impax Laboratories LLC resolving the lawsuits against MSN. The consolidated lawsuits against the remaining HETLIOZ ® Defendants were tried in March 2022. In December 2022, the Delaware District Court ruled that Teva and Apotex did not infringe U. S. Patent No. RE46, 604, and that the asserted claims of U. S. Patent Nos. RE46, 604; 9, 730, 910; 10, 149, 829; and 10, 376, 487 were invalid. We have appealed the decision to the U. S. Court of Appeals for the Federal Circuit **(Federal Circuit) and in May 2023, a three- judge panel of the Federal Circuit affirmed the Delaware District Court' s ruling. In August 2023, the Federal Circuit denied our request for a rehearing. In January 2024, we filed a petition for a writ of certiorari with the U. S. Supreme Court to review the Federal Circuit' s decision** . We have also filed Hatch- Waxman lawsuits in U. S. District Court for the District of New Jersey against each of Teva and Apotex and in the U. S. District Court for the Southern District of Florida against Apotex, in each case, asserting infringement of a method of administration patent that was not litigated in the Delaware District Court. **The New Jersey cases have been transferred to the**

Delaware District Court, where they remain pending. This litigation does not affect the sale of HETLIOZ ® in the E. U. and there is no generic litigation pending outside of the U. S. with respect to HETLIOZ ®. Furthermore, the litigation does not relate to the HETLIOZ LQ ® oral suspension formulation. See Note ~~16~~ **17** , Legal Matters, to the consolidated financial statements in Part II, Item 8 of this Annual Report and the risk factor entitled " We are, 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, " in Part I, Item 1A of this Annual Report, each of which is incorporated herein by reference, for additional information. In Europe, the law provides for 10 years of data exclusivity (with the potential for an additional year if a medicine is developed for a significant new indication). In addition, Europe provides for 10 years of market exclusivity for orphan indications. As such, in Europe, data or market exclusivity will provide protection for HETLIOZ ® for at least 10 years from approval. It is also possible that the protection through a basic patent (i. e., a patent that protects a product as such, a process to obtain a product, or an application of a product) in Europe could be extended for up to five years by the issuance of a supplementary protection certificate (SPC). A completed Pediatric Investigation Plan (PIP) could further extend SPC protection for an additional six months or the market exclusivity in an orphan indication for two additional years. Thus, a PIP could provide a total of 12 years of market exclusivity for an orphan indication. The European Patent Office has granted our patent application directed to the 20 mg / day dose. This patent will expire in 2027 and provides the basis for an SPC. Other pending patent applications in Europe, if granted, may offer additional protection for HETLIOZ ®. 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, could provide exclusivity for such indications and methods of treatment. The NCE patent for Fanapt ®, which expired in 2016 in the U. S. and in 2010 in other countries, was owned by Sanofi. Other patents and patent applications relating to Fanapt ® are owned by ~~Vanda~~ **us** . Fanapt ® metabolites, formulations, genetic markers and uses are the subject of numerous patent filings in which protection has been sought in the U. S., Europe, and other markets. In November 2013, a U. S. patent (U. S. 8, 586, 610) 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 U. S. marketing exclusivity for Fanapt ®. Additional method of treatment patents have been issued in the U. S. and listed in the Orange Book, with the latest expiration date in December 2031. We have also filed and plan on filing additional patent applications covering the use of iloperidone (Fanapt ® active ingredient) LAI formulations. Patents for the microsphere LAI formulation of Fanapt ® expired in 2022 in some markets in Europe and will expire in 2024 in the U. S. Patents for the aqueous microcrystals LAI formulation of Fanapt ® expire in 2023 in the U. S. and in some markets in Europe. We have pending patent applications covering the use of iloperidone and plan on filing additional applications based on discoveries made throughout the development plan of this molecule. We filed several Hatch- Waxman lawsuits in the Delaware District Court against a number of generic company competitors asserting infringement of two of our Fanapt ® patents. The litigation has been resolved with respect to all but one of these competitors. See Note ~~16~~ **17** , Legal Matters, to the consolidated financial statements in Part II, Item 8 of this Annual Report and the risk factor entitled " We are, 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, " in Part I, Item 1A of this Annual Report, each of which is incorporated herein by reference, for additional information. In Europe, the law provides for 10 years of regulatory 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 the applicable regulatory exclusivity period in most European countries. Outside the U. S. and Europe, similar regulatory package protection periods may be available and could protect Fanapt ® from generic competition for varying numbers of years depending upon the country. **Janssen has obtained patent protection for PONVORY ® and its formulations in selected countries worldwide, including the U. S. and Canada. In December 2023, we acquired all rights that Janssen had in U. S. and Canadian patents related to PONVORY ®, pending U. S. and Canada patent applications related to PONVORY ®, and any further U. S. and Canadian derivative patents and patent applications arising from the foregoing patents and pending patent applications. Regulatory exclusivity (NCE) protecting PONVORY ® in the U. S. will expire on March 18, 2026. The NCE patent covering the active ingredient in PONVORY ® (Reissue Patent No. 43, 728) is set to expire on November 16, 2024, but an application for term extension pursuant to the Hatch- Waxman Act was submitted, which would extend this patent' s term to November 16, 2029 if granted. The U. S. Patent and Trademark Office has granted additional patents, including a further patent directed to a crystalline form of the active ingredient in PONVORY ®, which will expire in May 2032 in view of awarded patent term adjustment. The U. S. Patent and Trademark Office has also issued three method of treatment patents for PONVORY ®, which will expire between November 2024 and December 2035. Furthermore, on January 24, 2024, the U. S. Patent and Trademark Office issued a Notice of Allowance in the case of U. S. Pat. Appl. No. 17 / 962, 968, which covers other methods of treatment using the active ingredient in PONVORY ®. Once issued, this patent would be expected to expire on October 10, 2042. Also, a number of patent applications covering further methods of treatment remain pending at the U. S. Patent and Trademark Office. In Canada, the Patented Medicines (Notice of Compliance) Regulations (PM (NOC) Regulations) create a regime analogous to the Hatch- Waxman Act and link the regulatory approval process for generic and biosimilar drugs to the adjudication of innovator patent rights. To be eligible for protection under the PM (NOC) Regulations, patents must first be listed on the Patent Register in connection with an innovator' s drug submission to Health Canada. A generic or biosimilar manufacturer must then provide notice to the innovator of its plans to market a drug that it compared to the innovator' s patented drug in the Health Canada approval process. Within 45 days of receiving such a notice of allegation, an innovator drug company may commence patent infringement proceedings against the generic or biosimilar**

manufacturer. The commencement of an action by the innovator under the PM (NOC) Regulations may stay Health Canada' s regulatory approval of the generic or biosimilar drug for a period of 24 months. It is also possible that protection through a patent (i. e., a patent claiming a medicinal ingredient, or the combination of all medicinal ingredients, or uses thereof) in Canada can be extended for up to two years by the issuance of a Certificate of Supplementary Protection (CSP). Health Canada' s Patent Register lists Canadian Patent Nos. 2545582, 2740313, and 2968180 for PONVORY ®, which are respectively directed to the active ingredient in PONVORY ®, the crystalline form of that active ingredient, and methods of treatment. These listed patents will respectively expire November 16, 2024; October 19, 2029; and April 29, 2036 in view of the CSP. Canada also employs a data exclusivity regime for innovative drugs that provides an eight- year period of data protection from the date of market approval by Health Canada. An additional six months of data exclusivity is provided for drugs studied in clinical trials relating to use in pediatric populations. Drug submissions seeking approval based on a comparison to an innovative drug cannot be filed during the first six years of the data exclusivity period. Generic or biosimilar drug submissions remain on hold until expiry of the innovator' s data protection term, unless the innovative product is a patented drug subject to further protection under the PM (NOC) Regulations. Canada has no distinct drug submission process for biosimilar or orphan drug products. Lilly owns the NCE patent as well as patent applications directed to polymorphic forms of, and methods of making tradipitant. This patent protection was sought in the U. S. and in other countries worldwide. These patents and patent applications have been licensed to us. The NCE patent covering tradipitant ~~expires~~ **expired** in April 2023, except in the U. S., where it expires normally in June 2024, subject to any extension that may be received under the Hatch- Waxman Act. We have filed additional patent applications based on discoveries made during recent studies with tradipitant. 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. 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 product candidates. Novartis owns the NCE 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. 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. The NCE patent ~~expires~~ **expired** normally in 2023 in the U. S., Europe, and other markets. Aside from the NCE patents and other in- licensed patents discussed above, we have obtained or filed numerous patents and patent applications, most of which have been filed in key markets including the U. S., relating to our products and product candidates. In addition, we have filed numerous other patent applications 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, relevant 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. Marketing and Sales HETLIOZ ® capsules were approved in the U. S. for the treatment of Non- 24 in January 2014 and HETLIOZ ® capsules and oral suspension were approved for the treatment of nighttime sleep disturbances in SMS in December 2020. We commercially launched HETLIOZ ® capsules in the U. S. in April 2014 and the oral suspension in March 2021. Additionally, HETLIOZ ® capsules were approved in the E. U. for the treatment of Non- 24 in totally blind adults in July 2015 and, in August 2016, we commercially launched HETLIOZ ® in Germany. Given the range of potential indications for HETLIOZ ®, we may pursue one or more partnerships for the development and commercialization of HETLIOZ ® worldwide. Fanapt ® oral tablets were approved in the U. S. for the treatment of schizophrenia in May 2009 and commercially launched in the U. S. in January 2010. We continue to explore the regulatory path and commercial opportunity for Fanapt ® oral formulation in other regions. **PONVORY ® tablets were approved in the U. S. for the treatment of RMS in adults in March 2021 and commercially launched in the U. S. by Janssen in April 2021. PONVORY ® tablets were approved in Canada for the treatment of RMS in adults in April 2021 and commercially launched in Canada by Janssen in November 2021. We acquired the U. S. and Canadian rights to PONVORY ® in December 2023 from Janssen. Janssen will continue PONVORY ® operations during a transition period, following which, regulatory and supply responsibilities will be transitioned to us.** Major Customers Our revenues are generated from product sales and are concentrated with **two** specialty pharmacies ~~, including Accredo (a subsidiary of Express Scripts)~~ and **three** ~~OptumRx (a subsidiary of UnitedHealth Group), and~~ wholesalers ~~, including AmerisourceBergen Drug Corporation, Cardinal Health, Inc~~ . ~~, and McKesson Corporation. These~~ **There were** five major customers **that** each accounted for more than 10 % of total revenues for ~~2022~~ **2023** and, as a group, represented ~~87~~ **80** % of total revenues for the year ended December 31, ~~2022~~ **2023** . 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 **® and PONVORY** ® are as follows: • For HETLIOZ ® in the treatment of nighttime sleep disturbances in SMS, there are no FDA approved direct competitors. For HETLIOZ ® in the treatment of Non- 24, Teva has launched at risk, and the FDA has approved the Abbreviated New Drug Applications (ANDA) for Apotex and MSN. In addition, sedative- hypnotic treatments for certain sleep related disorders include, Ambien ® (zolpidem) by Sanofi (including Ambien CR ®), Lunesta ® (eszopiclone) by ~~Sunovion Pharmaceuticals Inc~~ **Woodward Pharma Services** ., Rozerem ® (ramelteon) by Takeda Pharmaceuticals Company Limited, Silenor ® (doxepin) by Currax Pharmaceuticals LLC, Belsomra ® (suvorexant) by Merck & Co., Inc., Dayvigo ® (lemborexant) by Eisai Inc., generic products such as **agomelatine,** zaleplon, 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 Laboratories Limited, 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 LAI formulation Risperdal Consta ® and Invega ® (paliperidone), including the LAI formulation Invega ® Sustenna ®, each by Johnson & Johnson, the LAI formulation Zyprexa ® RelprevvTM (olanzapine) by ~~Lilly~~ **Cheplapharm** , Abilify ® (aripiprazole) by Otsuka America Pharmaceutical Inc., Abilify Maintena ® (the LAI formulation of Abilify ®) by Lundbeck / Otsuka America Pharmaceutical Inc., Geodon ® (ziprasidone) by Viatris, Inc., Saphris ® (asenapine) by **Allergan** ~~AbbVie Inc.~~ , Latuda ® (lurasidone) by Sunovion Pharmaceuticals Inc., Rexulti ® (brexpiprazole) by Lundbeck / Otsuka America Pharmaceutical, Inc., Aristada ® (aripiprazole lauroxil) extended- release injectable suspension by Alkermes, plc, Vraylar ® (cariprazine) by AbbVie Inc., Perseris ® (risperidone) extended- release injectable suspension by Indivior plc, Caplyta ® (lumapteperone) by Intra- Cellular Therapies, Inc., Lybalvi ® (olanzapine and samidorphan) by Alkermes, plc, and generic clozapine and quetiapine, as well as the typical antipsychotics haloperidol, chlorpromazine, thioridazine, and sulpiride (all of which are generic). **• For PONVORY ® in the treatment of RMS, the competitors include Avonex ® (interferon beta- 1a), Tysabri ® (natalizumab) and Plegridy ® (peginterferon beta- 1a), all by Biogen Inc., Vumerity ® (diroximel fumerate) by Biogen Inc. / Alkermes, plc, Betaseron ® (interferon beta- 1b) by Bayer Healthcare Pharmaceuticals Inc., Rebif ® (interferon beta- 1a) and Mavenclad ® (cladribine), both by Merck KGaA, Extavia ® (interferon beta- 1b) and Mayzent ® (siponimod), both by Novartis AG, Lemtrada ® (alemtuzumab) by Sanofi, Ocrevus ® (ocrelizumab) by Roche Holding AG / Biogen Inc., Zeposia ® (ozanimod) by BMS, Briumvi ® (ubiltuximab) by TG Therapeutics, Inc., Kesimpta ® (ofatumumab) by Novartis, Tyruko ® (natalizumab) by Sandoz Group AG and generic dimethyl fumarate, fingolimod, glatiramer acetate and teriflunomide.** 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. Manufacturing We currently utilize a virtual supply manufacturing and distribution chain, meaning that 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. Instead, we contract with third parties to source critical raw materials and 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 ® capsules and Fanapt ® oral tablets. 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 (tasimelteon) for HETLIOZ ® to Patheon and have agreed to order from Patheon at least 80 % of the total expected yearly production of new units of HETLIOZ ® capsules. 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 had an initial term of five years and automatically renews 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 12 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 in 2014, 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 expected yearly production of new units of Fanapt ® tablets for the U. S. and other specified countries each year for the term of the agreement. Patheon is responsible for manufacturing the Fanapt ® 1, 2, 4, 6, 8, 10 and 12 mg tablets, conducting quality control and stability testing, and packaging the Fanapt ® tablets. The Fanapt ® manufacturing agreement had an initial term of five years and automatically renews 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 12 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. In December 2020, we entered into a non- exclusive manufacturing agreement for the manufacture of commercial supplies of both 48 **mL** and 158 mL HETLIOZ LQ ® bottles. The HETLIOZ LQ ® manufacturing agreement has an initial term of five years and automatically renews 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 12 months prior to the end of the then current term. **PONVORY ® is manufactured by third parties and supplied to Jannsen, which is currently distributing PONVORY ® pursuant to the terms of a transition agreement. During the transition period, Vanda and Janssen will transition supply responsibility for PONVORY ® to us.** Government Regulation Government authorities in the U. S. at the federal, state and local levels and in other countries extensively regulate, among other things, the research, development, testing, manufacture, quality control, approval, labeling, packaging, storage, recordkeeping, promotion, advertising, distribution, marketing and export and import of pharmaceutical products. A new drug must be approved by the FDA through the NDA process before it may be legally marketed in the U. S. The process of obtaining regulatory approvals and the subsequent compliance with applicable federal, state, local and foreign laws and regulations require the expenditure of substantial time and financial resources. Moreover, failure to comply with applicable requirements may result in, among other things, warning letters, clinical holds, civil or criminal penalties, recall or seizure of products, injunction, disbarment, partial or total suspension of production or withdrawal of the product from the market. Any judicial, administrative or other governmental enforcement action could have a material adverse effect on our business. U. S. government regulation U. S. drug development and regulation In the U. S., the FDA regulates drugs under the federal Food, Drug, and Cosmetic Act (FDCA) and related regulations. Drugs are also subject to other federal, state and local statutes and regulations. The process of obtaining regulatory approvals and the subsequent compliance with appropriate federal, state and local statutes and regulations requires the expenditure of substantial time and financial resources. Failure to comply with the applicable U. S. requirements at any time during the product development process, approval process or post- approval may subject an applicant to administrative or judicial sanctions. These sanctions could include the FDA' s refusal to approve pending applications, withdrawal of an approval, a clinical hold, warning letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, restitution, disgorgement or civil or criminal penalties. Any agency or judicial enforcement action could have a material adverse effect on our business. Once a drug candidate is identified for development, it enters the preclinical testing stage. Preclinical tests include laboratory evaluations of product chemistry, toxicity and formulation, as well as animal studies. An ~~Investigational New Drug (~~ IND ~~)~~ application sponsor must submit the results of the preclinical tests, together with manufacturing information and analytical data, to the FDA as part of the IND. The sponsor must also include a protocol detailing, among other things, the objectives of the first phase of clinical trials, the parameters to be used in monitoring the safety of the trial, and the effectiveness criteria to be evaluated should the first phase lend itself to an efficacy evaluation. Some preclinical testing may continue even after the IND is submitted. The IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA, within the 30- day time period, places the clinical trial on a clinical hold. Clinical holds also may be imposed by the FDA at any time before or during clinical trials due to safety concerns about on- going or proposed clinical trials or non- compliance with specific FDA requirements, and the trials may not begin or continue until the FDA notifies the sponsor that the hold has been lifted. All clinical trials must be conducted under the supervision of one or more qualified investigators in accordance with FDA good clinical practice (GCP) requirements, which include a requirement that all research subjects provide their informed consent in writing for their participation in any clinical trial. Clinical trials must be conducted under protocols detailing the objectives of the trial, dosing procedures, subject selection and exclusion criteria and the safety and / or effectiveness criteria to be evaluated. Each protocol must be submitted to the FDA as part of the IND, and timely safety reports must be submitted to the FDA and the investigators for serious and unexpected adverse events. An Institutional Review Board (IRB) at each institution participating in the clinical trial must review and approve each protocol before a clinical trial may commence at the institution and must also approve the information regarding the trial as well as the consent form that must be provided to each trial subject or his or her legal representative, monitor the study until completed and otherwise comply with all applicable IRB regulations. Human clinical trials are typically conducted in three sequential phases that may overlap or be combined in certain cases: • Phase I: The compound is initially introduced into healthy human subjects and tested for safety, dosage tolerance, absorption, metabolism, distribution and excretion and, if possible, to gain an early indication of its effectiveness. In most cases, initial Phase I clinical trials are conducted with healthy volunteers. However, where the compound being evaluated is for the treatment of severe or life-threatening diseases, such as cancer, and especially when the product may be too toxic to ethically administer to healthy volunteers, the initial human testing may be conducted on patients with the target disease or condition. Sponsors sometimes subdivide their Phase I clinical trials into Phase Ia and Phase Ib clinical trials. Phase Ib clinical trials are typically aimed at confirming dosage, pharmacokinetics and safety in a larger number of patients. Some Phase Ib studies evaluate biomarkers or surrogate markers that may be associated with efficacy in patients with specific types of diseases or conditions. • Phase II: This phase involves clinical trials in a limited patient population to identify possible adverse effects and safety risks, to preliminarily evaluate the efficacy of the product for specific targeted diseases or conditions and to confirm dosage tolerance and appropriate dosage. • Phase III: Phase III clinical trials are undertaken to further evaluate dosage, clinical efficacy and safety in an expanded patient population, generally at geographically dispersed clinical study sites. These clinical trials, often referred to as " pivotal " clinical trials, are intended to establish the overall risk- benefit ratio of the compound and provide, if appropriate, an adequate basis for product labeling. The FDA or the sponsor may suspend a clinical trial at any time on various grounds, including any finding that the research subjects or patients are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution if the clinical trial is not being conducted in accordance with the IRB' s requirements or if the drug has been associated with unexpected, serious harm to study subjects. In addition, clinical trials may

be overseen by a DSMB, an independent group of qualified experts organized by the sponsor. Depending on its charter, the DSMB may determine whether a trial may move forward at designated check points based on access to certain data from the trial. Post- approval trials may also be conducted after a drug receives initial marketing approval. These trials, often referred to as " Phase IV " trials, are used to gain additional experience from the treatment of patients in the intended therapeutic indication. In certain instances, the FDA may mandate the performance of such clinical trials as a condition of approval of an NDA. During the development of a new drug, sponsors are given several opportunities to meet with the FDA. These meetings can provide an opportunity for the sponsor to share information about the progress of the application or clinical trials, for the FDA to provide advice, and for the sponsor and the FDA to reach agreement on the next phase of development. These meetings may occur prior to the submission of an IND, at the end of Phase II clinical trials, or before an NDA is ultimately submitted. Sponsors typically use the meetings at the end of the Phase II trials to discuss Phase II clinical results and present plans for the pivotal Phase III clinical trials that they believe will support approval of the new drug. Meetings at other times may be made upon request. Concurrent with clinical trials, companies typically complete additional, animal or other non- clinical studies, develop additional information about the chemistry and physical characteristics of the drug, and finalize a process for manufacturing the product in commercial quantities in accordance with the FDA' s current Good Manufacturing Practices (cGMP) requirements. The manufacturing process must consistently produce quality batches of the drug and, among other things, the manufacturer must develop methods for testing the identity, strength, quality and purity of the final drug. In addition, appropriate packaging must be selected and tested, and stability studies must be conducted to demonstrate the effectiveness of the packaging and that the compound does not undergo unacceptable deterioration over its shelf life. While the IND is active, progress reports summarizing the results of ongoing clinical trials and nonclinical studies performed since the last progress report must be submitted on at least an annual basis to the FDA, and written IND safety reports must be submitted to the FDA and investigators for serious and unexpected adverse events, findings from other studies suggesting a significant risk to humans exposed to the same or similar drugs, findings from animal or in vitro testing suggesting a significant risk to humans, and any clinically important, increased incidence of a serious adverse reaction compared to that listed in the protocol or investigator brochure. There are also requirements governing the submission of certain clinical trials and completed trial results to public registries. Sponsors of certain clinical trials of FDA- regulated products are required to register and disclose specified clinical trial registration and results information, which is made publicly available at www. clinicaltrials. gov. Failure to properly report clinical trial results can result in civil monetary penalties. Disclosure of clinical trial results can often be delayed until the new product or new indication being studied has been approved. U. S. review and approval process The results of product development, preclinical and other non- clinical studies and clinical trials, along with descriptions of the manufacturing process, analytical tests conducted on the chemistry of the drug, proposed labeling and other relevant information are submitted to the FDA as part of an NDA. The submission of an NDA is subject to the payment of substantial user fees; a waiver of which may be obtained under certain limited circumstances. The FDA reviews NDAs to determine, among other things, whether the product is safe and effective for its intended use and whether it is manufactured in a cGMP- compliant manner, which will assure and preserve the product' s identity, strength, quality and purity. Under Prescription Drug User Fee Act Amendments of 2022 ~~(PDUFA)~~, the FDA has a goal of 10 months from the date of " filing " of a standard, completed NDA for a new molecular entity to review and act on the submission. This review typically takes 12 months from the date the NDA is submitted to the FDA because the FDA has 60 days to make a " filing " decision after the application is submitted. The FDA conducts a preliminary review of all NDAs within the first 60 days after submission, before accepting them for filing, to determine whether they are sufficiently complete to permit substantive review. The FDA may request additional information rather than accept an NDA for filing. In this event, the NDA must be resubmitted with the additional information. The resubmitted application also is subject to review before the FDA accepts it for filing. The FDA may refer an application for a new drug to an advisory committee within the FDA. An advisory committee is a panel of independent experts, including clinicians and other scientific experts, that reviews, evaluates and provides a recommendation as to whether and under what conditions the application should be approved. The FDA is not bound by the recommendations of such an advisory committee, but it considers advisory committee recommendations carefully when making decisions. Before approving an NDA, the FDA will also inspect the facility where the product is manufactured. The FDA will not approve an application unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and are adequate to assure consistent production of the product within required specifications. Before approving an NDA, the FDA may also inspect one or more clinical trial sites to assure compliance with GCP requirements. After the FDA evaluates an NDA, it will issue an approval letter or a ~~complete response letter (CRL)~~. A CRL indicates that the review cycle of the application is complete, and the application will not be approved in its present form. A CRL usually describes the specific deficiencies in the NDA identified by the FDA and may require additional clinical data, such as an additional pivotal Phase III trial or other significant and time- consuming requirements related to clinical trials, nonclinical studies or manufacturing. If a CRL is issued, the sponsor must resubmit the NDA, addressing all of the deficiencies identified in the letter, or withdraw the application. Even if such data and information are submitted, the FDA may decide that the NDA does not satisfy the criteria for approval. An approval letter authorizes commercial marketing of the drug with prescribing information for specific indications. The Pediatric Research Equity Act (PREA) requires IND sponsors to conduct pediatric clinical trials for most drugs, for a new active ingredient, new indication, new dosage form, new dosing regimen or new route of administration. Under the PREA, original NDAs and supplements must contain a pediatric assessment unless the sponsor has received a deferral or waiver. The required assessment must evaluate the safety and effectiveness of the product for the claimed indications in all relevant pediatric subpopulations and support dosing and administration for each pediatric subpopulation for which the product is safe and effective. The sponsor or the FDA may request a deferral of pediatric clinical trials for some or all of the pediatric subpopulations. A deferral may be granted for several reasons, including a finding that the drug is ready for approval for use in adults before pediatric clinical trials are complete or that additional safety or effectiveness data needs to be

collected before the pediatric clinical trials begin. The FDA must send a non- compliance letter to any sponsor that fails to submit the required assessment, keep a deferral current or fails to submit a request for approval of a pediatric formulation. If a drug receives FDA approval, the approval may be limited to specific diseases and dosages, which could restrict the commercial value of the product. In addition, the FDA may require testing and surveillance programs to monitor the safety of approved products that have been commercialized, and may require a sponsor to conduct post- marketing clinical trials, which are designed to further assess a drug' s safety and effectiveness after NDA approval. The FDA may also place other conditions on approval, including a requirement for a risk evaluation and mitigation strategy (REMS) to assure the safe use of the drug. If the FDA concludes a REMS is needed, the sponsor of the NDA must submit a proposed REMS. The FDA will not approve the NDA without an approved REMS, if required. A REMS could include medication guides, physician communication plans or elements to assure safe use, such as restricted distribution methods, patient registries and other risk minimization tools. Any of these limitations on approval or marketing could restrict the commercial promotion, distribution, prescribing or dispensing of products. Marketing approval may be withdrawn for non- compliance with REMS or other regulatory requirements, or if problems occur following initial marketing. Post- approval requirements Once an approval is granted, the FDA may withdraw the approval if compliance with regulatory standards is not maintained or if problems occur after the drug reaches the market. Later discovery of previously unknown problems with a drug may result in restrictions on the drug or even complete withdrawal of the drug from the market. After approval, some types of changes to the approved drug, such as adding new indications, certain manufacturing changes and additional labeling claims, are subject to further FDA review and approval. Manufacturers and other entities involved in the manufacture and distribution of approved drugs are required to register their establishments with the FDA and certain state agencies and are subject to periodic unannounced inspections by the FDA and certain state agencies for compliance with cGMP regulations and other laws and regulations. Our approved products are, and any additional product manufactured or distributed by us following FDA approval will be, subject to continuing regulation by the FDA, including, among other things, recordkeeping requirements, reporting of adverse experiences with the drug, providing the FDA with updated safety and efficacy information, drug sampling and distribution requirements, complying with certain electronic records and signature requirements, and complying with FDA promotion and advertising requirements. The FDA strictly regulates labeling, advertising, promotion and other types of information regarding approved drugs that are placed on the market, and imposes requirements and restrictions on drug manufacturers, such as those related to direct- to- consumer advertising, the prohibition on promoting products for uses or in patient populations that are not described in the product' s approved labeling (known as " off- label use "), industry- sponsored scientific and educational activities and promotional activities involving the internet. Discovery of previously unknown problems or the failure to comply with the applicable regulatory requirements may result in restrictions on the marketing of a product for a certain indication or withdrawal of the product from the market as well as possible civil or criminal sanctions. Failure to comply with the applicable governmental requirements at any time during the product development process, approval process or after approval, may subject an applicant or manufacturer to administrative or judicial civil or criminal sanctions and adverse publicity. FDA sanctions could include refusal to approve pending applications, withdrawal of an approval, clinical holds on post- marketing clinical trials, enforcement letters, product recalls, product seizures, total or partial suspension of production or distribution, injunctions, fines, refusals of government contracts, mandated corrective advertising or communications with doctors, debarment, restitution, disgorgement of profits, or civil or criminal penalties, any of which could have a material adverse effect on our business. Under the Orphan Drug Act, the FDA may grant orphan drug designation to drugs intended to treat a rare disease or condition, generally a disease or condition that affects fewer than 200, 000 individuals in the U. S or, if it affects more than 200, 000 individuals in the U. S., there is no reasonable expectation that sales of the drug will be sufficient to offset the cost of developing and making the drug available in the U. S. Orphan drug designation must be requested before submitting an NDA. After the FDA grants orphan drug designation, the generic identity of the drug and its potential orphan use are disclosed publicly by the FDA. Orphan drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process. The first NDA applicant to receive FDA approval for a particular active ingredient to treat a particular disease with FDA orphan drug designation is entitled to a seven- year exclusive marketing period in the U. S. for that product, for that indication. During the seven- year exclusivity period, the FDA may not approve any other applications to market the same drug for the same disease, except in limited circumstances, such as a showing of clinical superiority to the product with orphan drug exclusivity. Orphan drug exclusivity does not prevent FDA from approving a different drug for the same disease or condition, or the same drug for a different disease or condition. Among the other benefits of orphan drug designation are tax credits for certain research and development expenses and a waiver of the NDA application user fee. Expedited development and review programs The FDA has a fast track designation program that is intended to expedite or facilitate the process for reviewing new drug products that meet certain criteria. Specifically, new drugs are eligible for fast track designation if they are intended to treat a serious or life-threatening disease or condition and demonstrate the potential to address unmet medical needs for the disease or condition. With regard to a fast track product, the FDA may consider for review sections of the NDA on a rolling basis before the complete application is submitted, if the sponsor provides a schedule for the submission of the sections of the NDA, the FDA agrees to accept sections of the NDA and determines that the schedule is acceptable, and the sponsor pays any required user fees upon submission of the first section of the NDA. Any product submitted to the FDA for approval, including a product with a fast track designation, may also be eligible for other types of FDA programs intended to expedite development and review, such as priority review and accelerated approval. A product is eligible for priority review if it is intended to treat a serious condition, and if approved, would provide a significant improvement in safety or efficacy compared to currently marketed products. The FDA will attempt to direct additional resources to the evaluation of an application for a new drug designated for priority review in an effort to facilitate the review. The FDA endeavors to review applications with priority review designations within six months of the filing date, as compared to 10 months for review of NDAs under its current PDUFA review goals. In addition, a

product may be eligible for accelerated approval. Drugs intended to treat serious or life- threatening diseases or conditions may be eligible for accelerated approval upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or lack of alternative treatments. As a condition of approval, the FDA may require that a sponsor of a drug receiving accelerated approval perform adequate and well- controlled post- marketing clinical trials. Drugs receiving accelerated approval may be subject to expedited withdrawal procedures if the sponsor fails to conduct the required post- marketing trials or if such trials fail to verify the predicted clinical benefit. In addition, the FDA currently requires as a condition for accelerated approval pre- approval of promotional materials, which could adversely impact the timing of the commercial launch of the product. Recently, the accelerated approval pathway has come under scrutiny within the FDA and by Congress. The FDA has put increased focus on ensuring that confirmatory studies are conducted with diligence and, ultimately, that such studies confirm the benefit. For example, the FDA has convened its Oncologic Drugs Advisory Committee to review what the FDA has called dangling or delinquent accelerated approvals where confirmatory studies have not been completed or where results did not confirm benefit. In addition, Congress is considering various proposals to potentially make changes to the accelerated approval pathway, including proposals to increase the likelihood of withdrawal of approval in such circumstances. The Food and Drug Administration Safety and Innovation Act established a category of drugs referred to as " breakthrough therapies " that may be eligible to receive breakthrough therapy designation. A sponsor may seek FDA designation of a compound as a " breakthrough therapy " if the product is intended, alone or in combination with one or more other products, to treat a serious or life- threatening disease or condition and preliminary clinical evidence indicates that the product may demonstrate substantial improvement over existing therapies on one or more clinically significant endpoints, such as substantial treatment effects observed early in clinical development. The designation includes all of the fast track program features, as well as more intensive FDA interaction and guidance. The breakthrough therapy designation is a distinct status from both accelerated approval and priority review, which can also be granted to the same drug if relevant criteria are met. If a product is designated as a breakthrough therapy, the FDA will work to expedite the development and review of such drug. Fast track designation, priority review and breakthrough therapy designation do not change the standards for approval but may expedite the development or approval process. However, even if a product qualifies for one or more of these programs, the FDA may later decide that the product no longer meets the conditions for qualification or decide that the time period for FDA review or approval will not be shortened. Marketing exclusivity The FDA provides periods of regulatory exclusivity, which provide the holder of an approved NDA limited protection from new competition in the marketplace for the innovation represented by its approved drug for a period of three or five years following the FDA' s approval of the NDA. Five years of exclusivity are available to NCEs. An NCE is a drug that contains no active moiety that has been approved by the FDA in any other NDA. An active moiety is the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt, including a salt with hydrogen or coordination bonds, or other noncovalent, or not involving the sharing of electron pairs between atoms, derivatives, such as a complex (i. e., formed by the chemical interaction of two compounds), chelate (i. e., a chemical compound), or clathrate (i. e., a polymer framework that traps molecules), of the molecule, responsible for the therapeutic activity of the drug substance. During the exclusivity period, the FDA may not accept for review or approve an ANDA or a 505 (b) (2) NDA submitted by another company that contains the previously approved active moiety. An ANDA or 505 (b) (2) application, however, may be submitted one year before NCE exclusivity expires if it includes a certification that the new product will not infringe the already approved product' s listed patents, or that such patents are invalid. If a product is not eligible for the NCE exclusivity, it may be eligible for three years of exclusivity. Three- year exclusivity is available to the holder of an NDA, including a 505 (b) (2) NDA, for a particular condition of approval, or change to a marketed product, such as a new formulation for a previously approved product, if one or more new clinical trials, other than bioavailability or bioequivalence trials, was essential to the approval of the application and was conducted or sponsored by the applicant. This three- year exclusivity period protects against FDA approval of ANDAs and 505 (b) (2) NDAs for the condition of the new drug' s approval. As a general matter, three- year exclusivity does not prohibit the FDA from approving ANDAs or 505 (b) (2) NDAs for generic versions of the original, unmodified drug product. Five- year and three- year exclusivity will not delay the submission or approval of a full NDA; however, an applicant submitting a full NDA would be required to conduct or obtain a right of reference to all of the preclinical studies and adequate and well- controlled clinical trials necessary to demonstrate safety and efficacy. Pediatric exclusivity is another type of marketing exclusivity available in the U. S. Pediatric exclusivity provides for an additional six months of marketing exclusivity attached to another period of exclusivity if a sponsor conducts clinical trials in children in response to a written request from the FDA. The issuance of a written request does not require the sponsor to undertake the described clinical trials. In addition, orphan drug designation, as described above, may offer a seven- year period of marketing exclusivity, except in certain circumstances. Orange Book listing, 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 Orange Book. Drugs listed in the Orange Book can, in turn be cited by potential competitors in support of approval of an 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 preclinical 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 an NCE, 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. Fraud and abuse laws and other U. S. regulatory matters Pharmaceutical companies are subject to broadly applicable fraud and abuse and other healthcare laws and regulations, in addition to the FDCA, that may constrain the business or financial arrangements and relationships through which these companies market, sell and distribute the products for which they obtain marketing approval. Some of the laws and regulations that may affect the ability of pharmaceutical companies 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 or recommending 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. 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. 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, known as " all- payor " laws. 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 recordkeeping and other requirements. Violations of the PDMA may result in criminal and civil penalties. In addition, the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act of 2010 (collectively known as the Affordable Care Act or ACA), discussed in more detail in Pharmaceutical Coverage, Pricing and Reimbursement and Healthcare Reform below, imposes annual reporting requirements related to sample distribution. False Claims Act The 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 False Claims Act, including promotion of pharmaceutical products for unapproved uses, providing free product to customers with the expectation that customers 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, the ACA 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 private individuals who may receive financial awards if their claims are successful. False Claims Act liability is potentially significant in the healthcare industry because the statute provides for treble damages and monetary penalties of $ 5, 500 to $ 11, 000 per false claim or statement, adjusted for inflation as applicable, with respect to violations occurring after November 2, 2015. 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 be awarded in litigation. These companies 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 of 1996

The 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. 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 privacy and 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 create, receive, maintain or transmit 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 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 Centers for Medicare & Medicaid Services (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~~ **or teaching hospitals** . Failure to report relevant data may result in civil fines and / or penalties. Foreign Corrupt Practices Act The 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. Violation of the FCPA could result in substantial civil and criminal penalties and remedies, including fines, disgorgement, and / or imprisonment. Analogous state laws Analogous state fraud and abuse laws and regulations, such as state anti- kickback and false claims laws, can apply to the business practices of pharmaceutical companies, including but not limited to research, distribution, sales or marketing arrangements and claims involving healthcare items or services reimbursed by non- governmental third- party payors and are generally broad and are enforced by many different federal and state agencies as well as through private actions. In addition to requiring reporting transfers of value, some states have imposed price reporting requirements. 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, and file periodic reports or disclosures with states. Compliance with these laws requires significant resources and companies that do not comply may face civil penalties or other consequences. Many state laws govern the privacy and security of personal information in specified circumstances. For example, the California Consumer Privacy Act (CCPA), which became effective on January 1, 2020, established a new legal framework governing covered businesses' collection and use of personal information of California residents by, among other things, creating an expanded definition of covered personal information, establishing new privacy rights for California residents, imposing an opt- in standard for certain disclosures of personal information about minors, and creating a new and potentially severe statutory damages framework for businesses subject to certain data breaches resulting from the failure to implement and maintain reasonable security procedures and practices. While properly collected clinical trial data and all protected health information governed by HIPAA are exempt from the current version of the CCPA, other personal information may be applicable and possible changes to the CCPA may broaden its scope. Foreign regulation Foreign drug development, review and approval processes Regardless of whether a sponsor obtains FDA approval for a product, it 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 U. S. drug development and 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, a sponsor may submit Marketing Authorization Applications 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. Companies face the risk that the resulting prices would be insufficient to generate an acceptable return. Foreign fraud and abuse laws and other regulatory matters Outside the U. S., companies 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 12 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, which can be costly and time- consuming. The collection and processing of personal data in the E. U. is governed by the General Data Protection Regulation (GDPR), which became applicable in May 2018. The GDPR **applies to personal data processing carried out by a controller or processor (i) located within the E. U. or (ii) targeting E. U. individuals regardless of controller or processor' s location. The GDPR** implements stringent operational requirements for **controllers and** processors ~~and controllers~~ of personal data, including, for example, **transparent information for the data subjects regarding the processing of their personal data, appropriate legal basis for processing personal data that may require to obtain the valid consent of the data subjects where applicable,** expanded ~~disclosure requirements about how personal information is to be used, strengthened~~ individual data subject rights, limitations on retention of personal data, increased requirements pertaining to ~~health~~ data **security** and **confidentiality** ~~pseudonymised (i. e., key- coded) data~~, shortened mandatory data breach notification ~~timelines~~ **with the competent supervisory authority** and higher standards for controllers **and processors** to demonstrate **their compliance with** ~~they~~ **the GDPR by documenting it** ~~have obtained valid consent for certain data processing activities~~. The GDPR provides that E. U. ~~member~~ **Member** ~~states~~ **States** may ~~make~~ **supplement the GDPR with** their own additional laws and regulations in relation to the **personal data** processing ~~of~~ **, in particular regarding sensitive personal data (e. g.,** genetic, biometric or health data **)** , which could result in differences between **E. U.** ~~member~~ **Member** ~~states~~ **States** , limit our ability to **collect,** use and share **such** personal data or cause our costs to increase, and harm our **reputation,** business and financial condition. Further, the U. K.' s exit from the E. U., often referred to as Brexit, has created uncertainty with regard to **applicable** data protection regulation in the U. K. While the transition period has now concluded, decisions are still to be made on how **to adapt the U. K.** data ~~transfers~~ **protection provisions further** to **Brexit** ~~and from the U. K. will be regulated~~. We are also subject to evolving and strict rules on the transfer of personal data out of the E. U. **, in particular to the U. S.** Failure to comply with **the** ~~E. U. data protection laws may result in significant fines, including~~ GDPR **results in** fines of up to the higher of € 20, 000, 000 or 4 % of total worldwide annual revenue of the preceding financial year, and other administrative penalties. Significant uncertainty exists as to the coverage and reimbursement status of products approved by the FDA and other government authorities. Sales of products will depend, in part, on the extent to which the costs of the products will be covered by third- party payors, including government health programs in the U. S. such as Medicare and Medicaid, commercial health insurers and managed care organizations. The process for determining whether a payor will provide coverage for a product may be separate from the process for setting the price or reimbursement rate that the payor will pay for the product once coverage is approved. Third- party payors are increasingly challenging the prices charged, examining the medical necessity, and reviewing the cost- effectiveness of medical products and services and imposing controls to manage costs. Third- party payors may also limit coverage to specific products on an approved list, or formulary, which might not include all of the approved products for a particular indication. In order to secure coverage and reimbursement for any product that might be approved for sale, a company may need to conduct expensive pharmacoeconomic studies in order to demonstrate the medical necessity and cost- effectiveness of the product, in addition to the costs required to obtain FDA or other comparable regulatory approvals. A payor' s decision to provide coverage for a drug product does not imply that the reimbursement rate ultimately paid will be adequate. Third party reimbursement may not be sufficient to maintain price levels high enough to realize an appropriate return on investment in product development. A primary trend in the U. S. healthcare industry and elsewhere is cost containment. There have been a number of federal and state proposals during the last several years regarding the pricing of pharmaceutical and biopharmaceutical products, limiting coverage and reimbursement for drugs and other medical products, government control and other changes to the healthcare system in the U. S. By way of example, the ACA was passed in 2010 and made significant changes to the coverage and payment for products under government health care programs. Among the provisions of the ACA of importance to pharmaceutical companies are: • an annual, nondeductible fee on any entity that manufactures or imports specified branded prescription drugs and biologic agents, apportioned among these entities according to their market share in certain government healthcare programs, although this fee does not apply to sales of certain products approved exclusively for orphan indications; • expansion of eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to certain individuals with income at or below 133 % of the federal poverty level; • expanded manufacturers' rebate liability under the Medicaid Drug Rebate Program (MDRP) by increasing the minimum rebate for both branded and generic drugs and extending rebate liability to prescriptions for individuals enrolled in Medicaid managed care plans; • introduced a new methodology for the reporting of average manufacturer price by manufacturers under the MDRP for drugs that are inhaled, infused, instilled, implanted or injected; • expanded the types of entities eligible for the 340B drug discount program; • established the Medicare Part D coverage gap discount program by requiring manufacturers to provide a point - of - sale - discount off the negotiated price of applicable brand drugs to eligible beneficiaries during their coverage gap period as a condition for the manufacturers' outpatient drugs to be covered under Medicare Part D; • established a new Patient - Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research; • added a requirement to annually report product samples that manufacturers and distributors provide to physicians; • expanded healthcare fraud and abuse laws, including the False Claims Act and the federal Anti- Kickback Statute, and enhanced penalties for noncompliance; and • established the Center for Medicare and Medicaid Innovation within CMS to test innovative payment and service delivery models to lower Medicare and Medicaid spending, potentially including prescription drug spending. Since its enactment, there have been judicial, executive and Congressional challenges to certain aspects of the ACA. In June 2021, the U. S. Supreme Court dismissed the most recent judicial challenge to the ACA brought by several states without specifically ruling on the constitutionality of the ACA. Other

legislative changes have been proposed and adopted since the ACA was enacted. These changes include the Budget Control Act of 2011, which, among other things, included aggregate reductions of Medicare payments to providers that started in 2013 and will stay in effect through 2031 unless additional congressional action is taken. More recently, in March 2021, President Biden signed into law the American Rescue Plan Act of 2021, which ~~will eliminate~~ **eliminated** the statutory Medicaid drug rebate cap, currently set at 100 % of a drug' s average manufacturer price, for single source and innovator multiple source drugs, beginning January 1, 2024. Additionally, in December 2020, CMS issued a final rule that materially modifies current MDRP regulations by, among other things, broadening the definitions of what constitutes a " line extension. " A " line extension " drug may be subject to a higher Medicaid rebate, and broadening this definition is likely to subject a greater number of drugs to the higher rebate. These new definitions became effective on January 1, 2022. Most significantly, in August 2022, President Biden signed the Inflation Reduction Act of 2022 (IRA) into law. This statute marks the most significant action by Congress with respect to the pharmaceutical industry since adoption of the ACA in 2010. Among other things, the IRA requires manufacturers of certain drugs to engage in price negotiations with Medicare (beginning in 2026), with prices that can be negotiated subject to a cap; imposes rebates under Medicare Part B and Medicare Part D to penalize price increases that outpace inflation (beginning October 1, 2022); and replaces the Medicare Part D coverage gap discount program with a new discounting program (beginning in 2025). The IRA permits the Secretary of the Department of Health and Human Services (HHS) to implement many of these provisions through guidance, as opposed to regulation, for the initial years. **On March 15, 2023 and June 30, 2023, HHS issued guidance regarding implementation of the Medicare drug price negotiation program in initial price applicability year 2026. HHS stated it would provide additional information in the future related to implementation for initial price applicability years 2027 and beyond. Several manufacturers and industry groups have challenged the drug price negotiation program for Medicare Parts B and D in federal court. These lawsuits are ongoing, and additional lawsuits may be filed in the future related to provisions of the IRA. It is unknown whether such litigation or other litigation, if brought, will be successful.** For ~~that~~ **these** and other reasons, it is currently unclear how the IRA will be effectuated, and while the impact of the IRA on the pharmaceutical industry cannot yet be fully determined, it is likely to be significant. The cost of prescription pharmaceuticals in the U. S. is likely to remain the subject of considerable discussion. There have been several Congressional inquiries and proposed and enacted legislation designed to, among other things, bring more transparency to drug pricing, review the relationship between pricing and manufacturer patient programs, reduce the costs of drugs under Medicare, and reform government program reimbursement methodologies for drug products. The likelihood of implementation of these and other reform initiatives is uncertain. In the coming years, additional legislative and regulatory changes could be made to governmental health programs that could significantly impact pharmaceutical companies and the success of our product candidates. We expect that healthcare reform measures that may be adopted in the future may result in more rigorous coverage criteria, new payment methodologies and additional downward pressure on the price that we receive for any approved product. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private payors. The implementation of cost containment measures or other healthcare reforms may prevent us from being able to generate revenue, attain profitability or commercialize our product candidates. At the state level, legislatures have increasingly passed legislation and implemented regulations designed to control pharmaceutical and biological product pricing, including price or patient reimbursement constraints, discounts, restrictions on certain product access, and marketing cost disclosure and transparency measures. Some measures encourage importation from other countries and bulk purchasing. In addition, regional health care authorities and individual hospitals are increasingly using bidding procedures to determine what pharmaceutical products and which suppliers will be included in their prescription drug and other health care programs. These measures could reduce the ultimate demand for our products, once approved, or put pressure on our product pricing. The IRA, as well as other federal, state and foreign healthcare reform measures that have been and may be adopted in the future, could have a material adverse effect on our business. These healthcare reforms, as well as other healthcare reform measures that may be adopted in the future, may result in additional reductions in Medicare and other healthcare funding, more rigorous coverage criteria, new payment methodologies and additional downward pressure on the price for any approved product and / or the level of reimbursement physicians receive for administering any approved product. Reductions in reimbursement levels may negatively impact the prices we can charge or the frequency with which products are prescribed or administered. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private payors. Similarly, pricing and reimbursement and the containment of healthcare costs has become a priority in a number of foreign jurisdictions. In the E. U., pricing and reimbursement schemes vary widely from country to country. Some countries provide that drug products may be marketed only after a reimbursement price has been agreed. Some countries may require the completion of additional studies that compare the cost- effectiveness of a particular drug candidate to currently available therapies, or so- called health technology assessments, in order to obtain reimbursement or pricing approval. For example, the E. U. provides options for its member states to restrict the range of drug products for which their national health insurance systems provide reimbursement and to control the prices of medicinal products for human use. E. U. member states may approve a specific price for a drug product or may instead adopt a system of direct or indirect controls on the profitability of the company placing the drug product on the market. Other member states allow companies to fix their own prices for drug products but monitor and control company profits. The downward pressure on health care costs in general, particularly prescription drugs, has become intense. As a result, increasingly high barriers are being erected to the entry of new products. In addition, in some countries, cross- border imports from low- priced markets exert competitive pressure that may reduce pricing within a country. Any country that has price controls or reimbursement limitations for drug products may not provide favorable reimbursement and pricing arrangements. See the risk factor entitled " If we fail to comply with our reporting and payment obligations under the Medicaid Drug Rebate Program or other governmental pricing programs in the U. S., we could be subject to additional reimbursement requirements, penalties, sanctions and fines which could have a material adverse effect on our business, financial

condition, results of operations and growth prospects ” in Part I, Item 1A of this Annual Report for additional information regarding our participation in federal healthcare programs and related compliance obligations. Human Capital We had ~~290~~ **203** full- time employees as of December 31, ~~2022~~ **2023** , compared with ~~278~~ **290** employees as of December 31, ~~2021~~ **2022** . 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. Our human capital objectives include attracting, training and retaining employees in a manner that supports innovation across our business. 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 incorporated by reference in this Annual Report and should not be considered a 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 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 business conduct and ethics, other corporate policies and procedures, and the charters of our Audit Committee, Compensation Committee and Nominating / Corporate Governance Committee are available at our corporate website at www. vandapharma. com. To access these documents from the main page of our website, click on “ Investor ” at the top of the page, then click on “ Learn More ” under “ Corporate Governance ” and then click on the desired document. We intend to satisfy the disclosure requirements under Item 5. 05 of Form 8 - K regarding amendments to, or waivers from, provisions of our code of business conduct and ethics by posting such information on the website address and location specified above. None of the information contained on our website or www. sec. gov is incorporated by reference into this Annual Report or any other report or document filed with the SEC unless expressly stated otherwise therein. 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 (Annual Report) or elsewhere. The following information should be read in conjunction with the consolidated financial statements and related notes in Part II, Item 8, Financial Statements and Supplementary Data and Part II, Item 7, Management’ s Discussion and Analysis of Financial Condition and Results of Operations. Because of the following risk factors, as well as other risk 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. We are dependent on the commercial success of HETLIOZ ® ~~and ,~~ Fanapt **® and PONVORY** ®. In the U. S., HETLIOZ ® competes with ~~a~~ generic ~~version~~ **versions** of HETLIOZ ® and we could experience increased generic competition in the near term. We are substantially dependent upon the commercial success of HETLIOZ ® capsules for the treatment of Non- 24- Hour Sleep- Wake Disorder (Non- 24) ~~and ,~~ HETLIOZ ® capsules and oral suspension (HETLIOZ LQ ®) for the treatment of nighttime sleep disturbances in Smith- Magenis Syndrome (SMS) ~~and ,~~ Fanapt ® oral tablets for the treatment of schizophrenia **and PONVORY ® oral tablets for the treatment of relapsing forms of multiple sclerosis (RMS) in adults** . 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, which was renewed in July 2020 for an unlimited duration, is valid in the 27 countries that are members of the European Union (E. U.), as well as European Economic Area members Iceland, Liechtenstein and Norway. In December 2020, the FDA approved our NDA and supplemental New Drug Application (sNDA) for HETLIOZ ® for the treatment of nighttime sleep disturbances in SMS in adults and children, respectively. HETLIOZ ® capsules, for adults with SMS, were immediately available after approval and the HETLIOZ LQ ® liquid formulation, for children with SMS, became available in March 2021. ~~On~~ **In** December ~~13,~~ 2022, the U. S. District Court for the District of Delaware (~~the~~ Delaware District Court) ruled in favor of certain generic drug companies in our patent litigation alleging that the companies’ generic versions of HETLIOZ ® capsules, for which they were seeking FDA approval, infringed our patents covering HETLIOZ ®. We ~~disagree with the ruling that certain claims of our patents are invalid or not infringed by the defendants and have~~ appealed the decision to the U. S. Court of Appeals for the Federal Circuit (Federal Circuit). ~~Teva Pharmaceuticals USA, Inc.~~ **In May 2023, a three- judge panel** ~~(Teva) has launched its generic version~~ of ~~HETLIOZ ® at risk in~~ **the Federal Circuit affirmed the Delaware District Court’ s ruling. In August 2023, the Federal Circuit denied our request for a rehearing. In January 2024, we filed a petition for a writ of certiorari with** the U. S **Supreme Court to review the Federal Circuit’ s decision** . The FDA has approved Abbreviated New Drug Applications (ANDA) for generic versions of ~~tasimelteon~~ **HETLIOZ ®** for **Teva Pharmaceuticals USA, Inc. (Teva),** Apotex Inc. (Apotex) and MSN Pharmaceuticals Inc. and MSN Laboratories Private Limited (MSN) **. Teva and Apotex have launched their generic versions of HETLIOZ ® at risk in the U. S., and MSN has launched its generic version as well** . HETLIOZ ® could face even more competition from **other** generic companies in the U. S. in the near term in light of the patent litigation rulings against us. Sales of generic versions of HETLIOZ ® **have resulted in and** could **continue to** result in a ~~significant~~

reduction in the demand for HETLIOZ ® and / or the price at which we can sell it **and / or create volatility in net product sales in future periods** , which would have a material and adverse impact on our revenues and results of operations. Unless and until ~~our appeal is~~ **we are able to** ~~successful~~ **successfully enforce our legal rights to exclusivity** , we may reduce the amount we spend with the intention of retaining the capability to ramp- up promptly ~~if we win upon appeal~~ . Our expansion and development of HETLIOZ ® outside the U. S. is generally not subject to the adverse patent ruling in the U. S. In the fourth quarter of 2014, we acquired the U. S. commercial rights to Fanapt ®, and began selling, marketing and distributing Fanapt ® in the U. S **. In December 2023, we acquired the U. S. and Canadian rights to PONVORY ® from Actelion Pharmaceuticals Ltd. (Janssen), a Johnson & Johnson Company. Janssen is responsible for the continued marketing and sale of PONVORY ® during a transition period until the regulatory and supply responsibilities for PONVORY ® are transitioned to us** . Our ability to generate significant product revenue from sales of HETLIOZ ® ~~and~~ **,** Fanapt ® ~~,~~ **and PONVORY ®** 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 ~~, including the impact of and outcome of our pending appeal of the December 2022 Delaware District Court' s ruling and the litigation that we recently commenced in the New Jersey and Florida District Courts~~ ; • 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; • gain broad acceptance of our products from physicians, health care payors, patients, pharmacists and the medical community; • minimize the impact of disruptions caused by public health crises; • 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 sales trajectories of our products; • 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; • maintain our existing regulatory approval for HETLIOZ ® in Europe **and PONVORY ® in Canada** ; • 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 ® **and commence commercial operations for PONVORY ®** , 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 **® and PONVORY** ®, which is uncertain. If our continued commercial efforts are not successful with respect to HETLIOZ ® ~~and~~ **,** Fanapt ® **and PONVORY ®** in the U. S., Europe **, Canada** or other jurisdictions in which these products may be approved for sale, our ability to generate increased product sales revenue may be adversely affected. 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. As a result of the decision in favor of generic drug companies in connection with our HETLIOZ ® patent litigation, we ~~could~~ **have** ~~face~~ **faced** ~~increased~~ generic competition in the near term and our revenues and results of operations could be **further** ~~materially and adversely~~ affected by the launch of ~~one or more~~ additional generic versions of HETLIOZ ® in the U. S. Between April 2018 and March 2021, we filed numerous Hatch- Waxman lawsuits in the Delaware District Court against Teva, MSN and Apotex asserting that our patents would be infringed by their generic versions of HETLIOZ ®. In January 2022, we entered into a license agreement with MSN and Impax Laboratories LLC (Impax), resolving the lawsuits against MSN. A trial was held in March 2022 in the Delaware District Court to resolve the consolidated lawsuits against the remaining companies (the Defendants). ~~On~~ **In** December ~~13,~~ 2022, following conclusion of the trial, the Delaware District Court issued its ruling in favor of the Defendants, finding that the Defendants' use of a generic HETLIOZ ®, for which they were seeking FDA approval, did not infringe one of our HETLIOZ ® patents and the asserted claims of certain of our other HETLIOZ ® patents were invalid. **We** ~~On December 14, 2022, we~~ appealed the decision to the Federal Circuit and **in May** ~~requested a stay of market entry by the Defendants while the appeal is pending. On December 16, 2022~~ **2023** , **a three- judge panel of** the Federal Circuit **affirmed** ~~granted a temporary injunction to prohibit market entry by Teva and Apotex until~~ the **Delaware District** ~~Federal Circuit entered its order on our~~ **Court ' s ruling** ~~motion for a stay pending appeal~~ . **In August** ~~On December 28, 2022~~ **2023** , the Federal Circuit denied our request for ~~an injunction~~ **a rehearing** . ~~Our appeal is pending before~~ **In January 2024, we filed a petition for a writ of certiorari with the U. S. Supreme Court to review** the Federal Circuit **' s decision** . Teva **and Apotex have since launched their generic versions at risk and MSN** has ~~since~~ launched its generic version ~~at risk~~ **as well** . The commercial launch of the generic ~~version~~ **versions** , and potential increased competition from additional generic entrants in the near term, **have resulted in and** could **continue to** have a material and adverse impact on our revenues and our results of operations. ~~MSN and Impax may be permitted to launch a generic version of HETLIOZ ® under certain limited circumstances pursuant to the license agreement with us.~~ Further, although we ~~are appealing the ruling of the Delaware District Court, and~~ are pursuing additional remedies in other courts, including seeking injunctions against Apotex and Teva, we may not be successful in any such efforts, which will be costly and time- consuming to pursue. Such efforts will also require considerable attention of management and could, even if ultimately successful, negatively impact our results of operations. See Note ~~16~~ **17** , Legal Matters, to the consolidated financial statements in Part II, Item 8 of this Annual Report and the risk factor entitled " We are, 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, " each of which is incorporated herein by reference, for additional information. In addition, while we believe that HETLIOZ ® is difficult to manufacture and that building capacity to manufacture HETLIOZ ® is time-consuming and expensive, which may limit the amount of tasimelteon supply available to generic companies, we do not have direct visibility into the supply levels of any of the generic companies and we rely on our own experience together with information from third parties, which information may not be reliable. The generic companies could potentially find or develop sources of qualified HETLIOZ ® supply that are not known to us and that are more efficient or inexpensive than our sources. Furthermore, generic companies could potentially convince our suppliers or third- party manufacturers to prioritize supply to the generic companies ahead of any applicable contractual commitments to supply us. Such circumstances could have a material and adverse impact on our revenues and results of operations directly in the U. S. and potentially outside of the U. S. as well if supply costs and availability are affected. Future performance of HETLIOZ ® ~~and~~ **,** Fanapt **® and PONVORY** ® may be impacted by a number of factors including competing products or unanticipated safety issues. If ~~either~~ HETLIOZ ® ~~or~~ **,** Fanapt **® or PONVORY** ® is not successful in gaining broad commercial acceptance, our business would be harmed. Future performance of HETLIOZ ® ~~and~~ **,** Fanapt **® and PONVORY** ® sales will be dependent on several factors, including our ability to educate physicians and to increase physician awareness of the benefits of our products relative to competing products. The degree of further market acceptance of any of our products, including with respect to new indications, 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: • the impact and outcome of our pending patent litigation and appeals efforts; • the commercialization and pricing of any generic version of HETLIOZ ® on the market; • 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; • market awareness of the condition to be treated; and • pricing and cost effectiveness. In addition, HETLIOZ ® ~~and~~ **,** Fanapt **® and PONVORY** ® 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 **® or PONVORY** ® from the market, our revenues would decline significantly and our business would be seriously harmed. With the ~~at risk~~ launch of ~~a~~ generic ~~version~~ **versions** of HETLIOZ ® and further generic versions possible, it may not be viable for us to invest in market education to grow the U. S. market and our ability to maintain current promotional efforts and attract favorable commercial terms in several aspects of our business will likely be adversely affected as we face increased generic competition. We are subject to uncertainty relating to pricing and reimbursement policies in the U. S., including recent and future health reform measures, which, if not favorable for our products, could hinder or prevent our products' commercial success. Our ability to commercialize our products successfully depends in part on the coverage and reimbursement levels with governmental authorities, private health insurers and other third- party payors. In determining whether to reimburse our products and at what level, third- party payors consider factors that include the efficacy, cost effectiveness and safety of our products, as well as the availability of other treatments including generic prescription drugs and over- the- counter alternatives. We expect to continue to face pressure to make unfavorable pricing modifications, such as discounts or rebates. Negotiating favorable reimbursement can be a time consuming and expensive process, and there is no guarantee that we will be able to reach pricing terms with third- party payors at levels that are profitable to us. Certain third-party payors also have reimbursement or coverage processes that we believe are difficult to navigate and require prior authorization for, or even refuse to provide, reimbursement for our products, and others may do so in the future. Our business may be materially adversely affected if our patients are not able to receive approval for reimbursement of our products from third- party payors on a broad, timely or satisfactory basis; if reimbursement is subject to difficult reimbursement or coverage processes or prior authorization requirements; or if reimbursement is not maintained at satisfactory levels. In addition, our business could be adversely affected if third- party payors limit or reduce the indications for, or conditions under which, or the patient populations for whom, our products may be reimbursed. Moreover, as discussed further below and above in Part I, Item 1 under the heading Pharmaceutical Coverage, Pricing and Reimbursement and Healthcare Reform, changes in insurance coverage or reimbursement levels by third- party payors, or in the type of such coverage held by patients may materially harm our business and commercialization efforts. We expect to experience pricing pressures in connection with the sale of our current and future products due to the healthcare reforms discussed below and above in Part I, Item 1 under the heading Pharmaceutical Coverage, Pricing and Reimbursement and Healthcare Reform, as well as the trend toward initiatives aimed at reducing healthcare costs, the increasing influence of managed care, the scrutiny of pharmaceutical pricing, the ongoing debates on reducing government spending and additional legislative proposals. There has been significant scrutiny of pharmaceutical pricing and the resulting costs of pharmaceutical products that could cause significant operational and reimbursement changes for the pharmaceutical industry. There have been a number of federal and state efforts to address drug costs, which generally have focused on increasing transparency around drug costs or limiting drug prices, price increases or other related costs. Healthcare reform efforts or any future legislation or regulatory actions aimed at controlling and reducing healthcare costs, including through measures designed to limit reimbursement, restrict access or impose unfavorable pricing modifications on pharmaceutical products, could impact our ability to obtain or maintain reimbursement for our products at satisfactory levels, or at all, which could materially harm our business and financial results. We have encountered third- party payors that refuse to cover or reimburse prescriptions written for HETLIOZ ® and patients who are unable to navigate the coverage or reimbursement processes established by these third- party payors. If this trend continues, the commercial success of HETLIOZ ® may be limited, and our business and results of operations may be materially harmed. We have encountered third- party payors that refuse to cover or reimburse prescriptions written for HETLIOZ ®. This rate may increase further as a result of the

recent entry into the market of generic versions of HETLIOZ ®. Additionally, we are aware of patients who are experiencing difficulties navigating coverage processes established by third- party payors, making it difficult for them to fill a prescription for HETLIOZ ®. The revenue that we receive from HETLIOZ ® is significantly less than it would be if third- party payors were to remove or lessen these reimbursement challenges and hurdles and approve a greater percentage of the prescriptions written for HETLIOZ ®. Our business may be materially adversely affected if this trend continues and large numbers of patients cannot fill their HETLIOZ ® prescriptions due to coverage or reimbursement challenges. If the FDA does not ~~accept~~ **approve** our tradipitant NDA ~~or sNDA filings~~ **filing** for the use of tradipitant for patients with gastroparesis ~~and~~ **or accept our sNDA filing for the use of tradipitant for** patients with motion sickness; **or** if the FDA determines that our clinical trial results for tradipitant for the treatment of gastroparesis or for the treatment of motion sickness do not demonstrate adequate safety and substantial evidence of efficacy ~~; or if the FDA does not approve an applicable PDUFA date~~ , continued development of tradipitant will be significantly delayed or terminated, our business will be significantly harmed, and the market price of our stock could decline. In February 2022, we announced results from our Phase III clinical study, VP- VLY- 686- 3301, evaluating the efficacy and safety of tradipitant in treating the symptoms of gastroparesis. The study did not meet its prespecified primary endpoint, which was the difference between drug and placebo on the change of the severity of nausea from baseline at week 12 of treatment. Both treatment arms showed significant improvements from baseline on nausea as well as the other core symptoms of gastroparesis. When restricting the analysis in the group of patients that used no rescue medications at baseline and adjusting for poor compliance, we identified strong evidence of a drug effect across a number of symptoms and across the duration of the study, including a significant and meaningful effect at the prespecified primary endpoint of nausea change at week 12. The FDA may not view this data as constituting substantial evidence of efficacy for tradipitant in any indication for the treatment of gastroparesis or its symptoms, for any length of treatment. ~~We are preparing for submission~~ **In May 2023, we announced positive results from the first Phase III study** of ~~an NDA for~~ tradipitant ~~for patients~~ **in motion sickness, confirming the previously reported results demonstrating that tradipitant is effective in the prevention of vomiting associated** with ~~gastroparesis~~ **motion sickness. Our second Phase III study of tradipitant in motion sickness is ongoing** . We have also initiated a Phase III clinical study of tradipitant for the treatment of motion sickness. Any adverse developments or results or perceived adverse developments or results with respect to our regulatory submission or the tradipitant clinical programs in any or all indications will significantly harm our business and could cause the market price of our stock to decline. Examples of such adverse developments include, but are not limited to: • the FDA determining that they believe additional clinical studies are required with respect to tradipitant for the treatment of gastroparesis or for the treatment of motion sickness; • safety, efficacy or other concerns arising from clinical or non- clinical studies in these programs; or • the FDA determining that the tradipitant clinical trial programs raise safety concerns or do not demonstrate substantial evidence of efficacy. We believe that tradipitant has a well- established safety profile, as demonstrated by the results of extensive testing in animals and humans. Despite these results, however, the FDA informed us in December 2018 that in order to treat patients beyond 12 weeks, we ~~will~~ **would** have to conduct a nine- month non- rodent chronic toxicity study. This currently limits our ability to collect safety data in humans for more than 12 weeks. The non- rodent study required by the FDA necessitates the sacrifice of dozens of animals and we have disputed the necessity of a nine- month non- rodent chronic toxicity study. In February 2019, we filed a lawsuit in the U. S. District Court for the District of Columbia (DC District Court) challenging the FDA' s position, but we ultimately did not prevail. Despite our disagreement with the FDA, the preclinical package has allowed us to continue to conduct all of the efficacy studies necessary for NDA filing. Moreover, in July 2020, the FDA authorized tradipitant through an expanded access program (EAP) for a single patient. An EAP allows a patient to request the use of tradipitant, prior to NDA approval, for up to six months with an option to request renewal. Since then, certain patients who experienced a benefit in tradipitant studies have requested and received expanded access, while others have been denied treatment under the EAP. The EAP is ongoing and a number of patients have initiated treatment. Although this EAP is not intended for data collection, we collect safety data from this cohort of expanded access patients and ~~plan to include~~ **included** this data in the NDA **that we submitted** for tradipitant for patients with gastroparesis **. In December 2023, the FDA accepted our NDA for tradipitant in gastroparesis for filing and set a PDUFA target action date of September 18, 2024. If approved, tradipitant will be the first novel drug to be approved by the FDA for the treatment of gastroparesis in over 40 years and tradipitant is the first novel drug to be accepted for review by the FDA for gastroparesis in over 30 years** . The FDA may disregard such safety data when reviewing the NDA. The lack of long- term (i. e., more than 12 weeks in humans) safety data would likely impact the FDA' s willingness to approve tradipitant for a chronic indication. However, because long- term safety data is not normally a requirement for short- term indications, and with a preclinical profile that has not precluded clinical development, we believe the package ~~is~~ **was** complete for any NDA filing to treat patients for 12 weeks or less. For example, the FDA has communicated to us that it is considering an indication for the short- term relief of nausea in gastroparesis. While this short- term indication is not preferred, we would consider accepting this limited indication while continuing to pursue a chronic indication. However, the FDA may not deem the safety information sufficient even for a short- term indication. Moreover, FDA authorization of an EAP is not a guarantee of or a step in obtaining full FDA approval of an NDA. Our business will be materially adversely impacted if we are not able to agree with the FDA on a regulatory path to approval for tradipitant ~~, we experience any delay in filing,~~ or the FDA delays or denies approval of NDA or sNDA filings for the treatment of gastroparesis or motion sickness. Financial instability or a general decline in economic conditions in the U. S. and other countries caused by political instability and conflict and economic challenges caused by general health crises such as the COVID- 19 pandemic have led to market disruptions, including significant volatility in commodity prices, credit and capital market instability and supply chain interruptions, which have caused record inflation globally and could adversely affect our operations **. Increased inflation may result in increases in our operating costs (including our labor costs), reduced liquidity and limits on our ability to access credit or otherwise raise capital on acceptable terms, if at all. In addition, the U. S. Federal Reserve has raised, and may again raise, interest**

rates in response to concerns about inflation, which coupled with reduced government spending and volatility in financial markets may have the effect of further increasing economic uncertainty and heightening these risks . Economic conditions, and uncertainty as to the general direction of the macroeconomic environment, are beyond our control and may make any necessary debt or equity financing more difficult, costly and dilutive. While we believe we have adequate capital resources to meet current working capital and capital expenditure requirements, an economic downturn or significant increase in our expenses could require additional financing on less than attractive rates or on terms that are excessively dilutive to existing stockholders. Failure to secure any necessary financing in a timely manner and on favorable terms could have a material adverse effect on our stock price and could require us to delay or abandon clinical development plans. As discussed in the risk factor entitled " We are subject to uncertainty relating to pricing and reimbursement policies in the U. S., including recent and future health reform measures, which, if not favorable for our products, could hinder or prevent our products' commercial success ", sales of our products are dependent, in large part, on reimbursement from government health administration authorities, private health insurers, distribution partners and other organizations. In the event of economic decline, these organizations may be unable to satisfy their reimbursement obligations or may delay payment. In addition, federal and state health authorities may further reduce Medicare and Medicaid reimbursements, and private insurers may further increase their scrutiny of claims. A reduction in the availability or extent of reimbursement could negatively affect our product sales and revenue. In addition, we rely on third parties for several important aspects of our business. For example, we use third parties for sales, distribution, medical affairs and clinical research, and we rely upon several single source providers of raw materials and contract manufacturers for the manufacture of our products. During challenging and uncertain economic times and in tight credit markets, there may be a disruption or delay in the performance of our third- party contractors, suppliers or partners. If such third parties are unable to satisfy their commitments to us, our business and results of operations would be adversely affected. Global health crises and pandemics, such as the ~~novel coronavirus (~~ COVID- 19 ~~)~~, could lead to the implementation of various responses, including government- imposed quarantines, travel restrictions and other public health safety measures that may negatively impact productivity and disrupt our business. Additionally, the COVID- 19 pandemic ~~has~~ caused global supply chain disruptions that may have lasting impacts and consequences that are difficult to predict. The COVID- 19 pandemic ~~has~~ impacted clinical research globally, including delays in our development programs. While our clinical trials have since resumed patient enrollment, we may experience future disruptions as a result **of the lasting effects** of the COVID- 19 pandemic or other health crises that could adversely impact our sales activities, supply chain, our ongoing and planned clinical trials, and other regulatory activities, including: • curtailment of our sales force or patient access to healthcare providers, which may reduce the number of prescription refills or new patient starts, thereby adversely affecting our revenues; • interruption of, or delays in receiving, supplies of the active pharmaceutical ingredients that our contract manufacturing organizations use to manufacture our products and any related interruption of, or delays in receiving, supplies of our products from these organizations, due to staffing shortages, production slowdowns or stoppages and disruptions in delivery systems; • delays or difficulties in clinical site initiation, including difficulties in recruiting clinical site investigators and clinical site staff; • diversion of healthcare resources away from the conduct of clinical trials, including the diversion of hospitals serving as our clinical trial sites and hospital staff supporting the conduct of our clinical trials; • delays or difficulties in enrolling patients in our clinical trials; • interruption of key clinical trial activities, such as clinical trial site data monitoring, due to limitations on travel imposed or recommended by federal or state governments, employers and others or interruption of clinical trial subject visits and study procedures (such as procedures that are deemed non- essential), which may impact the integrity of subject data and clinical study endpoints; • limitations on our employee resources or those of third- party clinical research organizations towards the development of our products, including because of sickness of employees or their families or the desire of employees to avoid contact with large groups of people; and • interruption or delays in the operations of regulatory agencies, which may impact review and approval timelines. ~~The COVID- 19 pandemic continues to rapidly evolve. The extent to which the pandemic may continue to impact our business, financial condition and results of operations will depend on future developments, which are highly uncertain and cannot be predicted with confidence, such as the duration and severity of the pandemic, the emergence of new variant strains of the virus, travel restrictions and social distancing practices, business closures or business disruptions and the effectiveness of actions taken in the U. S. and other countries to contain and treat the disease.~~ If the FDA does not approve our sNDAs for HETLIOZ ® for the treatment of jet lag disorder or insomnia ~~or~~ **,** continued development of tasimelteon for the treatment of jet lag disorder ~~is~~ **and insomnia will be** significantly delayed or terminated, our business will be significantly harmed, and the market price of our stock could decline. In December 2018, we announced that the FDA had accepted the HETLIOZ ® sNDA for the treatment of jet lag disorder. We received a complete response letter (CRL) in August 2019 in which the FDA asserted that the measures of the study were of unclear clinical significance and declined to approve our sNDA. We met with the FDA to discuss the CRL in a Post Action meeting and in 2022 we requested the opportunity for a hearing with the FDA on the approvability of the jet lag disorder sNDA. We filed a lawsuit against the FDA in September 2022 demanding that the FDA immediately publish in the Federal Register a notice of opportunity for a hearing on the jet lag disorder sNDA. The FDA then published the notice in the Federal Register in October 2022. We ~~are undergoing discussions~~ **have asked the U. S. District Court for the District of Columbia (DC District Court) to, among other things, compel the FDA to comply** with **its obligations and declare that its lack of compliance violates the FDCA and** the FDA **regulations. In January 2024, the DC District Court held an oral argument** on **dispositive cross- motions, following which** the ~~timing of such~~ **DC District Court granted our motion for summary judgment. The DC District Court ruled that the FDA violated the statute and ordered the FDA to either finally resolve our application or commence a** hearing **on or before March 5, 2024. Our lawsuit remains pending. We have asked the DC District Court to, among other things, compel the FDA to comply with its obligations and declare that its lack of compliance violates the FDCA and the FDA regulations** . In ~~November~~ **January** ~~2022~~ **2024** , ~~we announced~~ **the DC District Court held an oral argument on dispositive cross- motions, following which the DC District**

Court granted our motion for summary judgment. The DC District Court ruled that ~~we were preparing for~~ the ~~submission of~~ **FDA violated the statute** ~~an~~ **and ordered the FDA to either finally resolve our application or commence a hearing on or before March 5, 2024. Our lawsuit remains pending. In July 2023, the FDA accepted our** sNDA for HETLIOZ ® in ~~the treatment of~~ insomnia **for filing and set a Prescription Drug User Fee Act (PDUFA) target action date of March 4, 2024 for its decision** . Any additional adverse developments or results or perceived adverse developments or results with respect to our regulatory ~~submission~~ **submissions** for jet lag disorder or insomnia will significantly harm our business and could cause the market price of our stock to decline. Examples of such adverse developments include, but are not limited to: • the FDA determining that additional clinical studies are required with respect to the jet lag disorder or insomnia programs; • safety, efficacy or other concerns arising from clinical or non- clinical studies in the jet lag disorder or insomnia programs, or the manufacturing processes or facilities used for the jet lag disorder program; or • the FDA determining that the jet lag disorder or insomnia programs raise safety concerns or ~~does~~ **do** not demonstrate substantial evidence of efficacy. If the FDA does not approve our sNDA for Fanapt ® for the treatment of bipolar I disorder, our business will be significantly harmed, and the market price of our stock could decline. In December 2022, we announced Fanapt ® was effective in the treatment of acute manic and mixed episodes associated with bipolar I disorder in adults in a randomized double- blind placebo controlled Phase III study. ~~We intend to submit an~~ **In August 2023, the FDA accepted our** sNDA for Fanapt ® **in** ~~for the treatment of acute manic and mixed episodes associated with~~ bipolar I disorder in adults ~~in~~ **for filing and set a PDUFA target action date of April 2,** ~~2023~~ **2024 for its decision** . Any additional adverse developments or results or perceived adverse developments or results with respect to our regulatory submission for bipolar I disorder will significantly harm our business and could cause the market price of our stock to decline. Examples of such adverse developments include, but are not limited to: • the FDA determining that additional clinical studies are required with respect to the bipolar I disorder program; • safety, efficacy or other concerns arising from clinical or non- clinical studies in the bipolar I disorder program, or the manufacturing processes or facilities used for the bipolar I disorder program; or • the FDA determining that the bipolar I disorder program raises safety concerns or does not demonstrate substantial evidence of efficacy. We may enter into third- party collaborations from time to time in order to develop and 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. While we are not currently party to any material commercial collaborative arrangements, 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, our business, results of operations or financial condition could be adversely affected. The ~~at risk~~ launch of ~~a~~ generic ~~version~~ **versions** of HETLIOZ ® and further generic competition may make it more difficult for us to identify or attract third- party collaborators and obtain favorable commercial terms in any such agreement or arrangement. 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~~ **may** have significant discretion in determining the efforts and resources that they will apply to these collaborations. We expect that the risks 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 that 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. Any such termination or expiration with respect to our future collaborations could adversely affect us financially as well as harm our business reputation. Even after we 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 are developing and the effectiveness of our 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. Generic competition may also adversely affect our ability to grow our markets and obtain acceptance of our products in the marketplace. We **have just recently completed the acquisition of PONVORY ® and our ability to commercialize PONVORY ® in the U. S. and Canada and transition regulatory and supply responsibility to us is uncertain, and we may not realize all of the**

anticipated benefits of the acquisition, those benefits make take longer to realize than expected or we may encounter significant integration difficulties. We acquired the U. S. and Canadian rights to PONVORY ® in December 2023. Our ability to realize the anticipated benefits of the acquisition will depend, to a large extent, on our ability to integrate PONVORY ® into our business and realize anticipated growth opportunities and synergies. We will be required to devote significant management attention and resources to integrating this product into our business. The process may be disruptive to our business and the expected benefits may not be achieved within the anticipated time frame, or at all. The failure to meet the challenges involved and to realize the anticipated benefits of the acquisition could adversely affect our business, financial condition and results of operations. Our ability to realize the anticipated benefits of the transaction will require us to overcome a number of difficulties, including, among others: • the diversion of management attention to integration matters; • difficulties in achieving anticipated business opportunities and growth prospects from the acquisition; • challenges related to public and market perception of PONVORY ® and / or our acquisition of the product; • delays or other difficulties with the transition of regulatory and supply responsibilities for PONVORY ® to us from Janssen; and • potential unknown liabilities, adverse consequences, unforeseen increased expenses or other unanticipated problems associated with the acquisition. Many of these factors are outside of our control, and any one of them could result in increased costs, decreased expected revenues and further diversion of management time and energy, which could materially harm our business, financial condition and results of operations. In addition, we have no Canadian operations and no history of commercializing products in Canada. As a result, we will have to either build our own Canadian sales force or enter into an agreement with one or more third- party collaborators for the sale and distribution of PONVORY ® in Canada. There is no guarantee that we will be successful in building our own Canadian sales force or that we will be able to identify or enter into an agreement with any such third- party collaborator on favorable terms, or at all. All of these factors could decrease or delay the expected accretive effect of the acquisition and negatively impact our stock price and harm our business. As a result, it cannot be assured that the acquisition of PONVORY ® will result in the full realization of the benefits anticipated from the transaction within the anticipated time frames or at all. We rely on outsourcing arrangements for a significant portion of our activities, including distribution, preclinical and clinical research and development, data collection and analysis and manufacturing. 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 ®, HETLIOZ LQ ® ~~or~~ Fanapt **® or PONVORY** ® supply chains could materially affect our level of success in commercializing these products, 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 ®, HETLIOZ LQ ® ~~or~~ **,** Fanapt **® or PONVORY** ®, 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 by regulatory authorities 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 ®, HETLIOZ LQ ® ~~or~~ **,** Fanapt **® or PONVORY** ® requires a lengthy regulatory and commercial process, including FDA approval of chemistry, manufacturing and controls (CMC) changes, 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. If we fail to comply with our reporting and payment obligations under the Medicaid Drug Rebate Program or other governmental pricing programs in the U. S., we could be subject to additional reimbursement requirements, penalties, sanctions and fines which could have a material adverse effect on our business, financial condition, results of operations and growth prospects. In U. S. markets, our ability to commercialize our products successfully, and to attract commercialization partners for our products, should we choose to do so, 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 therefore participate in, and have drug price reporting, payment, and other compliance obligations under, these programs. We participate in the Medicaid Drug Rebate Program (MDRP). Under the MDRP, 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). If we become aware that our MDRP submissions for a prior period were incorrect or have changed as a result of recalculation of the pricing data, we must resubmit the corrected data for up to three years after those data originally were due. Such restatements and recalculations increase our costs for complying with the laws and regulations governing the MDRP and the 340B program discussed below. Pursuant to the IRA, certain figures we report under the MDRP will also be used to compute rebates under Medicare Part D triggered by price increases that outpace inflation. If we fail to provide information timely or are found to have knowingly submitted false information to CMS, we may be subject to civil monetary penalties and other sanctions, including termination from the MDRP. Federal law requires that any company that participates in the MDRP also participate in the Public Health Service Act' 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 is administered by the Health Resources and Services Administration (HRSA) and requires us to agree to charge statutorily defined covered entities no more than the 340B " ceiling price " for our covered drugs when used in an outpatient setting. These 340B covered entities include a variety of community health clinics and other entities that receive health services grants from the Public Health Service, as well as **certain small rural hospitals and** hospitals that serve a disproportionate share of low- income patients. The ACA expanded the 340B program to include

additional entity types: certain free- standing cancer hospitals, critical access hospitals, rural referral centers and sole community hospitals, but exempts drugs designated under section 526 of the Federal Food, Drug and Cosmetic Act as " orphan drugs " from the ceiling price requirements for these covered entities. The 340B ceiling price is calculated using a statutory formula, which is based on pricing data we report under the MDRP and the rebate amount for the covered outpatient drug as calculated under the MDRP. In general, products subject to Medicaid price reporting and rebate liability are also subject to the 340B ceiling price requirement. We must report 340B ceiling prices to HRSA on a quarterly basis, and HRSA publishes them to 340B covered entities **and state Medicaid programs** . HRSA has finalized regulations regarding the calculation of the 340B ceiling price and the imposition of civil monetary penalties on manufacturers that knowingly and intentionally overcharge covered entities for 340B eligible drugs. HRSA has also finalized an administrative dispute resolution process through which 340B covered entities may pursue claims against participating manufacturers for overcharges. **A recent court decision in the District Court of South Carolina, Genesis Health Care, Inc. v. Becerra, found that HRSA' s definition of " patient " as applied to the 340B Program was too broad and may result in covered entities expanding the number of individuals considered eligible to receive drugs purchased through the 340B Program, resulting in higher volumes of drugs purchased at the discounted 340B ceiling price.** In addition, legislation may be introduced that, if passed, would further expand the 340B program, such as adding further covered entities or requiring participating manufacturers to agree to provide 340B discounted pricing on drugs when used in an inpatient setting. In order for products to be eligible for coverage under the Medicaid and Medicare Part B programs and to be purchased by certain federal agencies and grantees, we must also participate in the Department of Veterans Affairs Federal Supply Schedule (FSS), pricing program. As a participant, we must list our 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 we are required to 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. If a manufacturer participating in the FSS program fails to provide timely information or is found to have knowingly submitted false information, the manufacturer may be subject to civil monetary penalties. Individual states continue to consider and have enacted legislation to limit the growth of healthcare costs, including the cost of prescription drugs and combination products. A number of states have either implemented or are considering implementation of drug price transparency legislation that may prevent or limit our ability to take price increases at certain rates or frequencies. Requirements under such laws include advance notice of planned price increases, reporting price increase amounts and factors considered in taking such increases, wholesale acquisition cost information disclosure to prescribers, purchasers, and state agencies, and new product notice and reporting. Such legislation could limit the price or payment for certain drugs, and a number of states are authorized to impose civil monetary penalties or pursue other enforcement mechanisms against manufacturers for the untimely, inaccurate, or incomplete reporting of drug pricing information or for otherwise failing to comply with drug price transparency requirements. If we are found to have violated state law requirements, we may become subject to penalties or other enforcement mechanisms, which could have a material adverse effect on our business. 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. 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, or fail to submit pricing data on a timely basis, we may be subject to significant civil monetary penalties. 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 MDRP. 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. Efforts to ensure that our business arrangements with third parties, and our business generally, will comply with applicable healthcare laws and regulations may involve substantial costs. It is possible that governmental authorities will conclude that our business practices may not comply with current or future statutes, regulations, agency guidance or case law involving applicable fraud and abuse or other healthcare laws and regulations. If our operations are found to be in violation of any of these laws or any other governmental regulations that may apply to us, we may be subject to significant civil, criminal and administrative penalties, damages, fines, imprisonment, exclusion from government funded healthcare programs, such as Medicare and Medicaid, and the curtailment or restructuring of our operations. In addition, the requirements and penalties described above may affect our ability to profitably sell any product for which we obtain marketing approval. We are subject to ongoing regulatory obligations and oversight of our products, and any failure by us to maintain compliance with applicable regulations may result in adverse consequences including the suspension of the manufacturing, marketing and sale of our respective products, the incurrence of significant additional expense and other limitations on our ability to commercialize our respective products. We are subject to ongoing regulatory requirements and review, including periodic audits pertaining to the development, manufacture, labeling, packaging, adverse event reporting, distribution, storage, marketing, promotion, recordkeeping and export of our products. Failure to comply with such regulatory requirements or the later discovery of previously unknown problems with the manufacture, distributions and storage of our products, or our third- party contract manufacturing facilities or processes by which we manufacture our products may result in restrictions on our ability to develop, manufacture, market, distribute or sell our products, including potential withdrawal of our products from the market. Any such restriction could slow or stop production development or result in decreased sales, damage to our reputation or the initiation of lawsuits against us or our third- party contract manufacturers. We may also be subject to additional sanctions, including, but not limited, to the following: • Warning letters, public warnings and untitled letters; • Court- ordered seizures or injunctions; • Civil or criminal penalties, or criminal prosecutions; • Variation, suspension or withdrawal of regulatory approvals for our products; •

Changes to the package insert of our products, such as additional warnings regarding potential side effects or potential limitations on the current dosage or administration; • Requirements to communicate with physicians and other customers about concerns related to actual or potential safety, efficacy, or other issues involving our products; • Implementation of risk mitigation programs and post- approval obligations; • Restrictions on our continued manufacturing, marketing, distribution or sale of our products; • Temporary or permanent closing of the facilities of our third- party contract manufacturers; • Interruption or suspension of clinical trials; and • Refusal by regulators to consider or approve applications for additional indications. Any of the above sanctions could have a material adverse impact on our revenues or our reputation, and cause us to incur significant additional expenses. In addition, if our products face any safety or efficacy issues, including drug interaction problems, under the federal Food, Drug, and Cosmetic Act (FDCA), the FDA has broad authority to force us to take any number of actions, including, but not limited to, the following: • Requiring us to conduct post- approval clinical studies to assess product efficacy or known risks or new signals of serious risks, or to evaluate unexpected serious risks; • Mandating changes to a product' s label; • Requiring us to implement a risk evaluation and mitigation strategy (REMS) where necessary to assure safe use of the drug; or • Removing an already approved product from the market. Further, our partners, including our licensors, are subject to similar requirements and obligations as well as the attendant risks and uncertainties. If our partners, including our licensors, suffer material and adverse effects from such risks and uncertainties, our rights and benefits for our licensed products could be negatively impacted, which could have a material adverse effect on our business. If our products are marketed or distributed in a manner that violates federal or state healthcare fraud and abuse laws, marketing disclosure laws or other federal or state laws and regulations, we may be subject to civil or criminal penalties. In addition to FDA and related regulatory requirements, our general operations, and the research, development, manufacture, sale and marketing of our products, are subject to extensive additional federal and state healthcare regulation, including the federal Anti- Kickback Statute, the Prescription Drug Marketing Act, and the federal False Claims Act (FCA), the federal Health Insurance Portability and Accountability Act of 1996, the federal Physician Payment Sunshine Act and the Foreign Corrupt Practices Act (and their state analogues), as discussed above in Part I, Item 1 under the heading Government Regulation- Fraud and abuse laws and other U. S. regulatory matters. If we or our partners, such as licensors, fail to comply with any federal and state laws or regulations governing our industry, we could be subject to administrative, criminal and civil penalties and a range of regulatory actions that could adversely affect our ability to commercialize our products, harm or prevent sales of our products, or substantially increase the costs and expenses of commercializing and marketing our products, all of which could have a material adverse effect on our business, financial condition and results of operations. In recent years, CMS has been actively proposing and implementing changes to the list of business practices that are protected by safe harbors. There is inherent risk and uncertainty in any changing regulatory environment as companies work to transition business practices to conform with new regulations. Our activities relating to the sale and marketing of our products may be subject to scrutiny under these laws, and private individuals have been active in bringing so- called " whistleblower " lawsuits on behalf of the government (as Relators) under the FCA and similar regulations in other countries. In addition, incentives exist under applicable U. S. law that encourage employees and physicians to report violations of rules governing promotional activities for pharmaceutical products. These incentives have led to, and could continue to lead to, FCA lawsuits, which attempt to recoup moneys paid by government agencies and extract penalties from manufacturers. For example, federal enforcement agencies have recently pursued enforcement actions against pharmaceutical companies' product and patient assistance programs, including relationships with specialty pharmacies, and support for charitable foundations providing patients with co- pay assistance. In addition, Relators have filed lawsuits involving manufacturer reimbursement support services as well as promotion of pharmaceutical products beyond labeled claims. Some FCA lawsuits have resulted in government enforcement authorities obtaining significant civil and criminal settlements. Such lawsuits, whether with or without merit, are typically time- consuming and costly to defend. Such suits may also result in related shareholder lawsuits, which are also time- consuming and costly to defend. See Note ~~16~~ **17** , Legal Matters, to the consolidated financial statements in Part II, Item 8 of this Annual Report, which is incorporated herein by reference, for information regarding ongoing litigation related to similar matters. Further, the FDA and other regulatory agencies strictly regulate the promotional claims that may be made about prescription products. A product may not be promoted for uses that are not approved by the FDA as reflected in the product' s approved labeling. The FDA also regulates the content of promotional material, including, among other things, the presentation of efficacy information, the types of comparative claims that can be made to distinguish products from those with similar indications, and the balance of risk information provided. For drug products that are approved by the FDA under the FDA' s accelerated approval regulations, unless otherwise informed by the FDA, the sponsor must submit promotional materials at least 30 days prior to the intended time of initial dissemination of the promotional materials, which delays and may negatively impact a company' s ability to implement changes to its marketing materials, thereby negatively impacting revenues. For other products, the FDA does not review promotional materials prior to dissemination but does issue " Untitled Letters " or " Warning Letters " if it objects to content that has been used promotionally. The FDA may also withdraw approval of drug products under certain conditions. In particular, the FDA may withdraw approval of a drug if, among other things, the promotional materials are false or misleading, or other evidence demonstrates that the drug is not shown to be safe or effective under its conditions of use. In recent years, in addition to federal legislation related to transparency reporting of transfers of value to healthcare providers and healthcare organizations, several states have enacted legislation requiring pharmaceutical companies to file periodic reports. Several states have adopted legislation to require pharmaceutical companies to establish marketing and promotional compliance programs or codes of conduct or to file periodic reports with the state or make periodic public disclosures on sales, marketing, pricing, clinical trials, and other activities. Several states have also adopted laws that prohibit certain marketing- related activities, including the provision of gifts, meals or other items to certain healthcare providers. We have developed and implemented a corporate compliance program based on what we believe are current best practices in the pharmaceutical industry; however, relevant compliance laws are broad in scope and

there may not be regulations, guidance or court decisions that definitively interpret these laws in the context of particular industry practices. We cannot guarantee that we, our employees, our partners, our consultants or our contractors are or will be in compliance with all federal and state regulations. If we, our partners, or our representatives fail to comply with any of these laws or regulations, a range of fines, penalties or other sanctions and regulatory actions could be imposed on us, including, but not limited to, restrictions on how we market and sell our products, significant fines, exclusions from government healthcare programs, including Medicare and Medicaid, litigation, or other sanctions. Even if it is not determined that we have violated these laws, government investigations into these issues typically require the expenditure of significant resources and generate negative publicity, which could also have a material adverse effect on our business, financial condition and results of operations. Such investigations or suits have resulted in, and may continue to result in, related shareholder lawsuits, which can also have a material adverse effect on our business. Our partners, including our licensors, are subject to similar requirements and obligations as well as the attendant risks and uncertainties. If our partners, including our licensors, suffer material and adverse effects from such risks and uncertainties, our rights and benefits for our licensed products could be negatively impacted, which could have a material adverse effect on our business. HETLIOZ ® is 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 that 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 ®, particularly in light of the recent entry into the market of ~~a~~ generic ~~version~~ **versions** of 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; 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. Our future success will depend on our 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 preclinical 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 approval by the FDA or foreign regulators 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 other biotechnology companies, including major pharmaceutical companies. Our products may also compete with new products currently under development by others or with products that 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 ® **, PONVORY ®** 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. See Part I, Item 1, Competition, for a discussion of the primary competitors for HETLIOZ ® ~~and ,~~ Fanapt **® and PONVORY** ®. In addition, 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 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. In December 2022, the Delaware District Court ruled in favor of the Defendants in our patent litigation relating to the Defendants' filing of ANDAs for generic versions of HETLIOZ ® in the U. S. We ~~disagree~~ **appealed the decision to the Federal Circuit, and in May 2023, a three- judge panel of the Federal Circuit affirmed the Delaware District Court' s ruling. In August 2023, the Federal Circuit denied our request for a rehearing. In January 2024, we filed a petition for a writ of certiorari** with the **U. S Supreme** ~~ruling that the claims of our~~ **Court** ~~patents are invalid and are vigorously pursuing appeal~~ **to review the Federal Circuit' s decision** . ~~However,~~ **The FDA has approved ANDAs for** Teva **, Apotex and MSN, and Teva and Apotex have launched their generic versions of HETLIOZ ® at risk in the U. S., and MSN** has launched its generic version ~~of HETLIOZ~~

~~® at risk in the U. S. The FDA has~~ **as well. In addition,** ~~approved ANDAs for Apotex and MSN and~~ other potential competitors may be successful in obtaining ANDA approval and launching **their own** generic versions ~~as well~~. To obtain an ANDA approval for a generic drug, the generic company needs to show, among other things, that its version of the product is bioequivalent to the Reference Listed Drug (RLD). This usually requires the generic company to conduct bioequivalence studies comparing its product to the RLD, and to retain sufficient samples of the RLD used in testing after a study is complete. In recent years, U. S. federal lawmakers and the FDA have considered proposals and enacted legislation to facilitate the generic drug company' s access to samples and foster the generic competition. For example, the Creating and Restoring Equal Access to Equivalent Samples Act (CREATES Act) allows a biosimilar or generic product developer to bring a civil action against a brand drug manufacturer for failing to provide samples of the brand product for comparative testing " on commercially reasonable, market- based terms. " The developer could receive injunctive relief and a monetary award " sufficient to deter the license holder from failing to provide other eligible product developers with sufficient quantities of a covered product on commercially reasonable, market- based terms " in certain cases. While the full impact of the CREATES Act is unclear at this time, its provisions do have the potential to facilitate the development and future approval of generic versions of our products, introducing generic competition that could have a material adverse effect on our business, results of operations and financial condition. Certain states have also taken similar actions. For example, in 2018, Maine passed a new law that requires brand drug manufacturers to make samples of drugs distributed in the state available for sale in Maine at a price no greater than wholesale acquisition cost and without any restriction that would block or delay a biosimilar and generic drug application in a manner inconsistent with federal law. The state may seek injunctive relief and attorney' s fees from a drug manufacturer who fails to comply with this requirement. The research, testing, manufacturing and marketing of products such as those that we have developed or that we 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 must demonstrate to the satisfaction of the applicable regulatory agency that, among other things, the product is safe and effective for its intended use. In addition, we must show that the manufacturing facilities used to produce such products are in compliance with current good manufacturing practices (cGMPs). The process of obtaining FDA and other required regulatory approvals and clearances can take many years and will require us to expend substantial time and capital. Despite the time and expense expended, regulatory approval is never guaranteed. The number of preclinical 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 preclinical and clinical trials in different ways than we 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 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 PDUFA 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 regulatory approval strategies or components of the regulatory filings, such as clinical trial designs. For example, if certain of our methods for analyzing trial data are not accepted by the FDA or the applicable foreign agency, we may fail to obtain regulatory approval for our products. Additionally, 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. 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. 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 ® and HETLIOZ LQ ® in the U. S. and HETLIOZ ® in the 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. **In December 2023, we acquired U. S. and Canadian rights to PONVORY ®, which had already been approved by the FDA and Health Canada, for the treatment of adults with RMS.** 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, or such products that are adverse to our business. The FDA and foreign agencies generally approve drugs for use in specific 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. 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 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. For example, despite the positive results

of ~~our~~ **the** completed trials for HETLIOZ ® ~~and~~ **,** Fanapt **® and PONVORY** ®, as well as the FDA' s approval of the NDA for HETLIOZ ® for the treatment of Non- 24 in January 2014, the NDA for Fanapt ® for the treatment of schizophrenia in May 2009, the EC' s grant of the centralized marketing authorization for HETLIOZ ® for the treatment of Non- 24 in totally blind adults in July 2015, ~~and~~ the FDA' s approval of the sNDA and NDA for HETLIOZ ® capsule and liquid formulation for the treatment of adults and children, respectively, with nighttime sleep disturbances in SMS in December 2020 **, and the NDA for PONVORY ® for the treatment of RMS in adults in March 2021 and Health Canada' s approval of PONVORY ® for the treatment of adults with RMS in April 2021** , 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 long after they are approved for commercial sale. 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, any of which could have a material adverse effect on our business, results of operations and financial condition. In addition, if after receiving marketing approval of a product, we or others identify undesirable side effects caused by such product, we could face one or more of the following: • regulatory authorities may require us to implement a REMS, such as the addition of labeling statements (e. g., " black box " warning or a contraindication); • regulatory authorities may withdraw their approval of the product; • we may be required to change the way the product is administered, conduct additional clinical trials or change the labeling of the product; and • our or the product' s reputation may suffer. Any of these events could prevent us from achieving or maintaining market acceptance of the affected product or could substantially increase the costs and expenses of commercializing the product, which in turn could delay or prevent us from generating significant revenues from its sale. 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. Preclinical 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 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 or by third parties on our behalf may not demonstrate sufficient safety and efficacy to obtain the requisite regulatory approvals for our products. Regulatory authorities may not permit us 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 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~~ • the impact of global health crises; **and** • governmental or regulatory delays and changes in regulatory requirements and guidelines. If we 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. We may not be able to achieve sustained profitability. We have been engaged in identifying and developing drug products since March 2003, which has required, and will continue to require, significant research and development expenditures. The continued commercialization of HETLIOZ ® ~~and~~ **,** Fanapt **® and PONVORY** ® will also require substantial additional expenditures. As of December 31, ~~2022~~ **2023** , we had an accumulated deficit of $ ~~157~~ **155** . ~~9~~ **4** million and we cannot estimate with precision the extent of our future income or loss. We may not succeed in maintaining or gaining additional market acceptance of HETLIOZ ® ~~and~~ **,** Fanapt **® and PONVORY** ® in the U. S. and we may not succeed in commercializing HETLIOZ ® or Fanapt ® outside of the U. S **or PONVORY ® in Canada** . 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, which depends on many factors, including but not limited to, our ability to obtain regulatory approval for our products and achieve success in commercializing them in the U. S., Europe **, Canada** and our other target jurisdictions, as well as other factors described in this Annual Report. In addition, the amount we spend on developing, obtaining and maintaining regulatory approval for and commercializing our products, among other expenditures described in this Annual Report, will impact our profitability. We have recorded deferred tax assets based on our assessment that we will be able to realize the benefits of our net operating losses and other favorable tax attributes. Realization of deferred tax assets involves significant judgments and estimates, which are subject to change and ultimately depends on generating sufficient taxable income of the appropriate character during the appropriate periods. Changes in circumstances may

affect the likelihood of such realization, which in turn may trigger the need for additional valuation allowance against our deferred tax assets and adversely affect our net income and financial condition. In addition, we are potentially subject to ongoing and periodic tax examinations and audits in various jurisdictions, including with respect to the amount of our net operating losses and any limitation thereon. An adjustment to such net operating loss carryforwards, including an adjustment from a taxing authority, could result in higher tax costs, penalties and interest, thereby adversely impacting our financial condition. **Certain** ~~In general, under Section 382~~ of **our tax attributes** ~~the Internal Revenue Code of 1986~~ , **including** ~~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~~ **credit carryforwards, would be subject to limitation under Section 382 and 383 should an ownership change as defined under Section 382 of** ~~other~~ -- **the** ~~tax assets~~ **Internal Revenue Code of 1986, as amended (IRC), occur. The limitation resulting from a " change in ownership " could affect our ability to utilize NOLs and credit carryforwards** (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 ~~net operating losses (~~NOLs ~~)~~ or ~~credits~~ - **credit carryforwards** could have a material adverse effect on our results of operations and cash flows. **An** ~~Ownership~~ **ownership** ~~changes~~ - **change** occurred in the ~~years~~ - **year** ended December 31, 2014 ~~and 2008~~ . We believe that the ownership ~~changes~~ - **change** 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 adequately 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 ~~2023~~ **2024** and beyond. It is uncertain whether cash provided by our operating activities, together with our existing funds, will be sufficient to meet our long- term operating needs. As of December 31, ~~2022~~ **2023** , our total cash and cash equivalents and marketable securities were $ ~~466~~ **388** . ~~9~~ **3** 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 **® and PONVORY** ®, as well as other products that may be approved, globally; • outcomes of ongoing and potential patent litigation ~~, including the outcome of our pending appeal of the December 2022 Delaware District Court' s ruling~~ ; • 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 and maintaining manufacturing capabilities for commercial quantities of our products; • the number of potential formulations and products in development; • progress with preclinical 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; • cost of evaluating and acquiring new products from third parties; • competing technological and market developments; • costs for recruiting and retaining employees and consultants; • 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, including potentially limiting our ability to license product rights or enter into product development collaborations. However, we may not be able to raise additional funds on acceptable terms, or at all. 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 (CROs) do not successfully carry out their duties or if we lose our relationships with CROs, our drug development efforts could be delayed. Our arrangements with CROs are critical to our success in bringing our products to the market. We are **generally** dependent on CROs, third- party vendors and investigators for preclinical 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 CROs 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 as set forth in 21 Code of Federal Regulations (C. F. R.) Part 58 and Good Clinical Practices as set forth in 21 C. F. R. Part 50, 54, and 312, and similar international 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. 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. In addition, if we are not able to continue to operate our business relationships in a manner that is sufficiently profitable for us and our suppliers, certain members of our supply chain could compete with us through supply to competitors, such as generic drug companies, through breach of our agreements or otherwise. 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. In May 2016, we entered into a manufacturing agreement with Patheon for the manufacture of commercial supplies of Fanapt ® tablets at Patheon' s Mississauga, Ontario, Canada manufacturing site. Additionally, in December 2020, we entered into a non- exclusive third- party manufacturing agreement for the manufacture of commercial supplies of HETLIOZ LQ ®. 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. Moreover, if the facilities of such manufacturers do not pass a pre- approval or post- approval plant inspection, the FDA will not grant approval for our products and may institute restrictions on the marketing or sale of our products. Similarly, if we change contract manufacturers, the FDA must approve these contract manufacturers or any other CMC changes before our products can be manufactured. **PONVORY ® is manufactured by third parties and supplied to Janssen, which is currently distributing PONVORY ® pursuant to the terms of a transition agreement. During the transition period, Vanda and Janssen will transition supply responsibility for PONVORY ® to us. If we, or Janssen during the transition period, are unable to acquire sufficient quantities of PONVORY ®, our sales of PONVORY ® would suffer adverse effects.** 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 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 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 clinical trials, including due to supply chain issues caused by global health crises, product testing, potential regulatory approval of our products and commercial scale manufacturing could be delayed, significantly affecting our ability to further develop and commercialize our products. If we or our manufacturers 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 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. 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. 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. If we lose key scientists or management personnel, or if we fail to recruit additional highly skilled personnel, our ability to identify, develop, and commercialize new products will be impaired. 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 of our products. We believe that we may be at a greater risk of product liability claims relative to other pharmaceutical companies because certain of our products are intended to treat central nervous system disorders, among others, 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 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 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 law and / or by guidelines established by the 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 ® capsules 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 an additional 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 others, 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. 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. Healthcare legislative reform measures or developments arising from changes in the political climate may have a material adverse effect on our business and results of operations. In the U. S., there have been and continue to be a number of legislative initiatives to contain healthcare costs. Most significantly, in August 2022, President Biden signed the IRA into law. This statute marks the most significant action by Congress with respect to the pharmaceutical industry since adoption of the ACA in 2010. Among other things, the IRA requires manufacturers of certain drugs to engage in price negotiations with Medicare (beginning in 2026), with prices that can be negotiated subject to a cap; imposes rebates under Medicare Part B and Medicare Part D to penalize price increases that outpace inflation (beginning October 1, 2022); and replaces the Medicare Part D coverage gap discount program with a new discounting program (beginning in 2025). The IRA permits the Secretary of the **Department of Health and Human Services (** HHS **)** to implement many of these provisions through guidance, as opposed to regulation, for the initial years. **On March 15, 2023 and June 30, 2023, HHS issued guidance regarding implementation of the Medicare drug price negotiation program in initial price applicability year 2026. HHS stated it would provide additional**

information in the future related to implementation for initial price applicability years 2027 and beyond. Several manufacturers and industry groups have challenged the drug price negotiation program for Medicare Parts B and D in federal court. These lawsuits are ongoing, and additional lawsuits may be filed in the future related to provisions of the IRA. It is unknown whether such litigation or other litigation, if brought, will be successful. For ~~that~~ **these** and other reasons, it is currently unclear how the IRA will be effectuated, and while the impact of the IRA on the pharmaceutical industry cannot yet be fully determined, it is likely to be significant. Healthcare reforms are discussed above in Part I, Item 1 under the heading Pharmaceutical Coverage, Pricing and Reimbursement and Healthcare Reform and in the risk factor entitled " We are subject to uncertainty relating to pricing and reimbursement policies in the U. S., including recent and future health reform measures, which, if not favorable for our products, could hinder or prevent our products' commercial success. " These healthcare reforms, as well as other healthcare reform measures that may be adopted in the future, may result in additional reductions in Medicare and other healthcare funding, more rigorous coverage criteria, new payment methodologies and additional downward pressure on the price for any approved product and / or the level of reimbursement physicians receive for administering any approved product which could affect our business strategy or commercial prospects. Reductions in reimbursement levels may negatively impact the prices we can charge or the frequency with which products are prescribed or administered. Any reduction in reimbursement from Medicare or other government programs may result in a similar reduction in payments from private payors. 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 also adversely affect our business. We are subject to stringent laws, rules, regulations, policies, industry standards and contractual obligations regarding data privacy and security in foreign jurisdictions and may be subject to additional related laws ~~and~~ **, rules,** regulations **, policies, industry standards and contractual obligations** in other jurisdictions into which we expand. Many of these **provisions** ~~laws and regulations~~ are subject to change and reinterpretation **depending on the jurisdiction** and could result in claims, changes to our business practices, monetary penalties, increased cost of operations or other harm to our business **activities** . The regulatory framework for privacy and personal information security issues worldwide is rapidly evolving and is likely to remain uncertain for the foreseeable future. Various foreign government bodies and agencies have adopted or are considering adopting laws, rules, regulations and standards limiting, or laws, rules, regulations and standards regarding, the collection, distribution, use, disclosure, storage, security and other processing of personal information. Outside of the U. S., legal requirements relating to the collection, storage, processing and transfer of personal data continue to evolve. For example, the collection and use of health data and other personal data is governed in the ~~European Union~~ **E. U.** by the General Data Protection Regulation (GDPR), which became applicable in May 2018. The GDPR **applies to personal data processing carried out by a controller or processor (i) located within the E. U. or (ii) targeting E. U. individuals regardless of controller or processor' s location. The GDPR** implements stringent operational requirements for **controllers and** processors ~~and controllers~~ of personal data, including, for example, **transparent information for the data subjects regarding the processing of their personal data, appropriate legal basis for processing personal data that may require to obtain the valid consent of the data subjects where applicable,** expanded ~~disclosure requirements about how personal information is to be used, strengthened~~ individual data subject rights, limitations on retention of personal data, increased requirements pertaining to ~~health~~ data **security** and **confidentiality** ~~pseudonymised (i. e., key- coded) data, shortened~~ mandatory data breach notification ~~timelines~~ **with the competent supervisory authority** and higher standards for controllers **and processors** to demonstrate **their compliance with** ~~they~~ **the GDPR by documenting it** ~~have obtained valid consent for certain data processing activities~~ . The GDPR provides that E. U. ~~member~~ **Member** ~~states~~ **States** may ~~make~~ **supplement the GDPR with** their own additional laws and regulations in relation to the **personal data** processing ~~of~~ **, in particular regarding sensitive personal data, (e. g.,** genetic, biometric or health data **)** , which could result in differences between **E. U.** ~~member~~ **Member** ~~states~~ **States** , limit our ability to **collect,** use and share **such** personal data **or cause our costs to increase, and harm our reputation, business and financial condition** . Failure to comply with the GDPR may result in fines up to **the higher of** € 20, 000, 000 or 4 % of the total worldwide annual revenue of the preceding financial year ~~, whichever is higher,~~ and other administrative penalties. The GDPR may increase our responsibility and liability in relation to **health data and other** personal data that we may **collect and** process, and we may be required to implement additional measures in an effort to comply with the GDPR and with other laws, rules, regulations and standards in the E. U., including those of E. U. Member States, relating to privacy and data protection. This may be onerous and if our efforts to comply with GDPR or other applicable E. U. laws, rules, regulations and standards are not successful, or are perceived to be unsuccessful, it could adversely affect our business. In July 2020, the European Court of Justice (ECJ) invalidated the E. U.- U. S. Privacy Shield, which had enabled the transfer of personal data from the E. U. to the U. S. for companies that had self- certified to the Privacy Shield. While we do not rely on the Privacy Shield, the ECJ decision also raised questions about the continued validity of the **EC** ~~European Commission~~ ' s Standard Contractual Clauses, on which we rely. E. U. regulators have issued additional guidance regarding considerations and requirements that we and other companies must consider and undertake when using the Standard Contractual Clauses. **The EC** ~~Although the European Commission~~ has presented a new set of Standard Contractual Clauses, ~~which are required~~ to be **included in agreements involving personal** ~~implemented, there are few, if any, viable alternatives to the Standard Contractual Clauses and it remains to be seen whether additional means for lawful~~ data transfers ~~will become available~~ **outside the E** . ~~The ECJ' s~~ **U. In addition, in July 2023, the European Commission adopted its adequacy** decision ~~and other regulatory guidance or~~ **for** ~~developments may impose additional obligations~~ **the E. U.- U. S. Data Privacy Framework (DPF). U. S. companies** with ~~respect to~~ the **DPF certification can lawfully** transfer ~~of~~ personal data from the E. U. to the U. S **. without additional transfer mechanisms. However** , ~~all~~ **the validity** of ~~which~~ **such mechanism is currently challenged by NYOB, an Austrian non- profit organization seeking to enforce digital rights (particularly privacy, and data protection rights) in the E. U. This uncertainty regarding the validity of the existing transfer mechanisms** could restrict our activities in those

jurisdictions, limit our ability to provide our products and services in those jurisdictions, require us to modify our policies and practices, and to engage in additional contractual negotiations, or increase our costs and obligations and impose limitations upon our ability to efficiently transfer personal data from the E. U. to the U. S **. for conducting our business activities** . Risks related to intellectual property and other legal matters 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. Even if our patent applications issue as patents, they may not issue in a form that will provide us with any meaningful protection, prevent competitors from competing with us or otherwise provide us with any competitive advantage. Our competitors may be able to circumvent our owned or licensed patents by developing similar or alternative technologies or products in a non- infringing manner. Our competitors may seek to market generic versions of any approved products by submitting ANDAs to the FDA in which they claim that patents owned or licensed by us are invalid, unenforceable and / or not infringed. In December 2022, the Delaware District Court ruled in favor of the Defendants in our patent litigation relating to the Defendants' filing of ANDAs for generic versions of HETLIOZ ® in the U. S. We ~~disagree~~ **appealed the decision to the Federal Circuit, and in May 2023, a three- judge panel of the Federal Circuit affirmed the Delaware District Court' s ruling. In August 2023, the Federal Circuit denied our request for a rehearing. In January 2024, we filed a petition for a writ of certiorari** with the **U. S Supreme** ~~ruling that the claims of our~~ **Court** ~~patents are invalid and are vigorously pursuing appeal~~ **to review the Federal Circuit' s decision. Please see Note 17, Legal Matters, to the consolidated financial statements in Part II, Item 8 of this Annual Report, which is incorporated herein by reference, for additional information** . Alternatively, our competitors may seek approval to market their own products similar to or otherwise competitive with our products. In these circumstances, we may need to defend and / or assert our patents, including by filing lawsuits alleging patent infringement. In any of these types of proceedings, a court or other agency with jurisdiction may find our patents invalid and / or unenforceable. Even if we have valid and enforceable patents, these patents still may not provide protection against competing products or processes sufficient to achieve our business objectives. The issuance of a patent is not conclusive as to its inventorship, scope, validity or enforceability, and our owned and licensed patents may be challenged in the courts or patent offices in the U. S. and abroad. Such challenges may result in loss of exclusivity or freedom to operate or in patent claims being narrowed, invalidated or held unenforceable, in whole or in part, which could limit our ability to stop others from using or commercializing similar or identical technology and products, or limit the duration of the patent protection of our technology and products. In addition, given the amount of time required for the development, testing and regulatory review of new product candidates, patents protecting such candidates might expire before or shortly after such candidates are commercialized. 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 rights 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 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. We have been and continue to be involved in number of lawsuits with a variety of generic drug manufacturers who have filed ANDAs relating to certain of our patents. In December 2022, the Delaware District Court ruled in favor of the Defendants in our patent litigation relating to the Defendants' filing of ANDAs for generic versions of HETLIOZ ® in the U. S. We ~~disagree~~ **appealed the decision to the Federal Circuit, and in May 2023, a three- judge panel of the Federal Circuit affirmed the Delaware District Court' s ruling. In August 2023, the Federal Circuit denied our request for a rehearing. In January 2024, we filed a petition for a writ of certiorari** with the **U. S Supreme** ~~ruling that the claims of our~~ **Court to review** ~~patents are invalid and are vigorously pursuing appeal. However, we may not be successful in this lawsuit and other~~ -- **the** ~~such lawsuits in the future~~ **Federal Circuit' s decision** . Please see Note ~~16~~ **17** , Legal Matters, to the consolidated financial statements in Part II, Item 8 of this Annual Report, which is incorporated herein by reference, for additional information. 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. The HETLIOZ ® U. S. new chemical entity (NCE) patent (the primary patent covering the product as a new composition of matter) received the full five- year patent term extension under the Hatch- Waxman Act and so, assuming that we continue to have rights under our license agreement with respect to this product, this patent in the U. S. expired in December 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 between 2033 and ~~2035~~ **2041** , and ~~three~~ **four** drug substance patents that expire in 2035. Additionally, the U. S. Patent and Trademark Office has issued a drug formulation patent for HETLIOZ LQ ® that will expire in 2040. The Fanapt ® U. S. NCE 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. 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. **With respect to PONVORY ®, an application for term extension of the NCE patent pursuant to the Hatch- Waxman Act is pending. Based on correspondence between FDA and the U. S. Patent and Trademark Office, we expect that the NCE patent' s term should be extended for the maximum amount of time, five years, which would extend the term of this patent until November 2029. The U. S. Patent and Trademark Office has granted additional patents, including a further patent directed to a crystalline form of the active ingredient in PONVORY ®, which will expire in May 2032 in view of awarded patent term adjustment. The U. S. Patent and Trademark Office has also issued three method of treatment patents for** In December 2022, the Delaware District Court ruled in favor of the Defendants in our patent litigation relating to the Defendants' filing of ANDAs for generic versions of HETLIOZ ® in the U. S. See Note ~~16~~ **17** , Legal Matters, to the consolidated financial statements in Part II, Item 8 of this Annual Report and the risk factor entitled " We are, 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, " each of which is incorporated herein by reference, for additional information. The E. U. provides that companies that receive regulatory approval for a new medicinal product will have a 10- year period of regulatory data protection and market protection for that product (with the possibility of a further one- year extension under certain conditions), beginning on the date of such European regulatory approval, regardless of when the European NCE patent covering such product expires. A generic version of the approved drug that refers to the approved drug' s regulatory data may not be marketed or sold in Europe during such market protection period. This legislation is of material importance with respect to Fanapt ®, since the European NCE 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. NCE 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. NCE 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. Such extensions may not be granted because of, for example, the failure to exercise due diligence during the testing phase or regulatory review process, the failure to apply within applicable deadlines, the failure to apply prior to expiration of relevant patents, or any other failure to satisfy applicable requirements. Moreover, the applicable time period or the scope of patent protection afforded could be less than we request. If we fail to receive such extensions or exclusive rights, our ability to prevent competitors from manufacturing, marketing and selling generic versions of our products will be materially impaired. Generic company competitors have received FDA approval of generic versions of HETLIOZ ® in the U. S. We are pursuing ~~an appeal~~ **U. S. Supreme Court review** of **the May 2023 decision of the Federal Circuit affirming** the December 2022 Delaware District Court decision that declared as invalid claims of a group of patents that protect our exclusivity in the U. S. The FDCA, as amended by the Drug Price Competition and Patent Term Restoration Act of 1984, as amended, or the Hatch- Waxman Amendments, permits the FDA to approve ANDAs for generic versions of brand name drugs like HETLIOZ ®. We refer to the process of generic drug applications as the " ANDA process. " The ANDA process permits competitor companies to obtain marketing approval for a drug product with the same active ingredient, dosage form, strength, route of administration, and labeling as the approved brand name drug, but without having to conduct and submit clinical studies to establish the safety and efficacy of the proposed generic product. In place of such clinical studies, an ANDA applicant needs to submit data demonstrating that its product is bioequivalent to the brand name product, usually based on pharmacokinetic

studies. As an alternate path to FDA approval for modifications of products previously approved by the FDA, an applicant may submit an NDA, under Section 505 (b) (2) of the FDCA (enacted as part of the Hatch- Waxman Amendments). This statutory provision permits the filing of an NDA where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference from the owner of the data. The Hatch- Waxman Amendments permit the applicant to rely upon the FDA findings of safety and effectiveness of a drug that has obtained FDA approval based on preclinical or clinical studies conducted by others. In addition to relying on FDA prior findings of safety and effectiveness for a referenced drug product, the FDA may require companies to perform additional preclinical or clinical studies to support approval of the modification to the referenced product. If an application for a generic version of a branded product or a Section 505 (b) (2) application relies on a prior FDA finding of safety and effectiveness of a previously- approved product including an alternative strength thereof, the applicant is required to certify to the FDA concerning any patents listed for the referenced product in the Orange Book. Specifically, the applicant must certify in the application that: I. there is no patent information listed for the reference drug; II. the listed patent has expired for the reference drug; III. the listed patent for the reference drug has not expired, but will expire on a particular date and approval is sought after patent expiration; or IV. the listed patent for the reference drug is invalid, unenforceable, or will not be infringed by the manufacture, use or sale of the product for which the ANDA or 505 (b) (2) NDA is submitted. The Hatch- Waxman Amendments require an applicant for a drug product that relies, in whole or in part, on the FDA' s prior approval of HETLIOZ ®, to notify us of its application, a " paragraph IV " notice, if the applicant is seeking to market its product prior to the expiration of the patents that both claim HETLIOZ ® and are listed in the Orange Book. A bona fide paragraph IV notice may not be given under the Hatch- Waxman Amendments until after the generic company receives from the FDA an acknowledgement letter stating that its ANDA is sufficiently complete to permit a substantive review. The paragraph IV notice is required to contain a detailed factual and legal statement explaining the basis for the applicant' s opinion that the proposed product does not infringe our patents, that the relevant patents are invalid, or both. After receipt of a valid notice, the branded product manufacturer has the option of bringing a patent infringement suit in federal district court against any generic company seeking approval for its product within 45 days from the date of receipt of each notice. If such a suit is commenced within this 45- day period, the Hatch- Waxman Amendments provide for a 30- month stay on FDA' s ability to give final approval to the proposed generic product, which period begins on the date the paragraph IV notice is received. Generally, during a period of time in which generic applications may be submitted for a branded product based on a product' s regulatory exclusivity status, if no patents are listed in the Orange Book before the date on which a complete ANDA application for a product (excluding an amendment or supplement to the application) is submitted, an ANDA application could be approved by FDA without regard to a stay. For products entitled to five- year exclusivity status, the Hatch- Waxman Amendments provide that an ANDA application may be submitted after four years following FDA approval of the branded product if it contains a certification of patent invalidity or non- infringement to a patent listed in the Orange Book. In such a case, the 30- month stay runs from the end of the five- year exclusivity period. Statutory stays may be shortened or lengthened if either party fails to cooperate in the litigation and it may be terminated if the court decides the case in less than 30 months. If the litigation is resolved in favor of the ANDA applicant before the expiration of the 30- month period, the stay will be immediately lifted and the FDA' s review of the application may be completed. Such litigation is often time- consuming and costly, and may result in generic competition if such patents are not upheld or if the generic competitor is found not to infringe such patents. Between April 2018 and March 2021, we filed numerous Hatch- Waxman lawsuits in the Delaware District Court against Teva, MSN and Apotex asserting that U. S. Patent Nos. RE46, 604 (~~' '~~ 604 Patent), 9, 060, 995, 9, 539, 234, 9, 549, 913, 9, 730, 910 (' 910 Patent), 9, 844, 241, 10, 071, 977, 10, 149, 829 (' 829 Patent), 10, 376, 487 (' 487 Patent), 10, 449, 176, 10, 610, 510, 10, 610, 511, 10, 829, 465, and 10, 611, 744 would be infringed by their generic versions of HETLIOZ ®, for which they were seeking FDA approval. In January 2022, we entered into a license agreement with MSN and Impax resolving the lawsuits against MSN. The license agreement grants MSN and Impax a non- exclusive license to manufacture and commercialize MSN' s version of HETLIOZ ® in the U. S. effective as of March 13, 2035, unless prior to that date **we** ~~the Company obtains~~ **obtain** pediatric exclusivity for HETLIOZ ®, in which case the license will be effective as of July 27, 2035. MSN and Impax may enter the market earlier under certain limited circumstances. **In January 2023, MSN and its commercial partner, Amneal Pharmaceuticals, Inc., informed us of their belief that such circumstances have occurred and have since launched their generic. We disagree with this position and continue to aggressively defend our legal rights to exclusivity for HETLIOZ ®. There is no guarantee, however, that we will be successful in our efforts.** The consolidated lawsuits against the remaining Defendants went to trial in March 2022. ~~On~~ **In** December ~~13,~~ 2022, the Delaware District Court ruled that Teva and Apotex did not infringe the ' 604 Patent, and that the asserted claims of the ' 604 Patent, ' 910 Patent, ' 829 Patent and ' 487 Patent were invalid. **We** ~~On December 14, 2022, we~~ appealed **the decision to the Federal Circuit and in May 2023, a three- judge panel of the Federal Circuit affirmed** the Delaware District Court' s **ruling** ~~decision to the Federal Circuit and requested an injunction prohibiting market entry by Teva and Apotex while the appeal is pending~~ . **In August** ~~On December 16, 2022~~ **2023** ~~, the Federal Circuit granted a temporary injunction to prohibit market entry by Teva and Apotex until the Federal Circuit entered its order on our motion for a stay pending appeal. On December 28, 2022~~ , the Federal Circuit denied our request for ~~an injunction, and Teva has since launched~~ a ~~generic version~~ **rehearing. In January 2024, we filed a petition for a writ** of ~~HETLIOZ ® at risk~~ **certiorari with the U. S. Supreme Court to review the Federal Circuit' s decision** . While we are pursuing additional remedies ~~beyond our pending appeal of the Delaware District Court' s decision~~ , we cannot be certain of the success, timing or efforts involved in connection with these efforts. If any of the generic manufacturers has adequate supply available and is successful, such generic competition in the short term could have a material and adverse impact on our revenues and our stock price. We may also face challenges to the validity of our patents through a procedure known as inter partes review. Inter partes review is a trial proceeding conducted through the Patent Trial and Appeal Board, of the U. S. Patent and Trademark Office. Such a proceeding could be introduced

against us within the statutory one- year window triggered by service of a complaint for infringement related to an ANDA filing or at any time by an entity not served with a complaint. Such proceedings may review the patentability of one or more claims in a patent on specified substantive grounds such as allegations that a claim is obvious on the basis of certain prior art. We intend to continue to vigorously enforce our intellectual property rights relating to HETLIOZ ®, but we cannot predict the outcome of the pending lawsuits, our appeal, or any subsequently filed lawsuits or inter partes review. See Note ~~16~~ **17** , Legal Matters, to the consolidated financial statements in Part II, Item 8 of this Annual Report and the risk factor entitled " We are, 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, " each of which is incorporated herein by reference, for additional information. Any significant degree of generic market entry would limit our U. S. sales, which would have a significant adverse impact on our business and results of operations. In addition, even if a competitor' s effort to introduce a generic product is ultimately unsuccessful, the perception that such development is in progress and / or news related to such progress could materially affect the perceived value of our company and our stock price. For example, our stock price suffered a significant decline following our announcement of the Delaware District Court' s ruling in favor of the Defendants. 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. Our commercial success depends in part on our not infringing the patents and proprietary rights of third parties. Third parties may assert that we are employing their proprietary technology without authorization. In addition, third parties may obtain patents in the future and claim that use of our technologies infringes upon these patents. Furthermore, parties making claims against us may obtain injunctive or other equitable relief, which could effectively block our ability to develop and commercialize one or more of our 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 Note ~~16~~ **17** , Legal Matters, to the consolidated financial statements in Part II, Item 8 of this Annual Report, incorporated herein by reference, we have initiated lawsuits to enforce our patent rights against certain generic pharmaceutical companies. General Risk Factors 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, ~~2022~~ **2023** and December 31, ~~2022~~ **2023** , the high and low sale prices of our common stock as reported on The Nasdaq Global Market varied between $ ~~6~~ **3** . ~~73~~ **30** and $ ~~16~~ **8** . ~~93~~ **15** . 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 level of success in commercializing our products; • our level of success in executing our commercialization strategies; • publicity regarding actual or potential litigation involving us and the outcome of any such litigation; • publicity regarding actual or potential testing or trial results relating to products under development by us or our competitors; • the outcome of regulatory review relating to products under development by us or our competitors; • regulatory developments in the U. S. and foreign countries; • newly enacted healthcare legislation or changes to existing legislation; • developments concerning any collaboration or other strategic transaction we may undertake; • announcements of patent issuances or denials, technological innovations or new commercial products by us or our competitors; • safety issues with our products or those of our competitors; • announcements of technological innovations or new therapeutic products or methods by us or others; • actual or anticipated variations in our quarterly operating results; • changes in estimates of our financial results or recommendations by securities analysts or failure to meet such financial expectations; • changes in government regulations or policies; • changes in patent legislation or patent decisions or adverse changes to patent law; • additions or departures of key personnel or members of our board of directors; • the publication of negative research or articles about our company, our business or our products by industry analysts or others; • market rumors or press reports; • publicity regarding actual or potential transactions involving us; and • economic, political and other external factors beyond our control. We have been and may in the future be subject to litigation, which could harm our stock price, business, results of operations and financial condition. We have been the subject of litigation in the past and may be subject to litigation in the future. In the past, following periods of volatility in the market price of their stock, many companies, including us, have been the subjects of securities class action litigation. Any such litigation can result in substantial costs and diversion of management' s attention and resources and could harm our stock price, business results of operations and financial condition. For example, our stock price suffered a significant decline following our announcement of the Delaware District Court' s ruling in favor of the Defendants. As a result of these factors, holders of our common stock might be unable to sell their shares at or above the price

they paid for such shares. If there are substantial sales of our common stock, our stock price could decline. A small number of institutional investors and private equity funds hold a significant number of shares of our common stock. Sales by these stockholders of a substantial number of shares, or the expectation of such sales, could cause a significant reduction in the market price of our common stock. In addition to our outstanding common stock, as of December 31, ~~2022~~ **2023** , there were a total of 6, ~~147~~ **697** , ~~756~~ **816** shares of our common stock that we have registered and are obligated to issue upon the exercise of currently outstanding options and settlement of restricted stock unit awards granted under our 2006 and 2016 Equity Incentive Plans. Upon the exercise of these options or settlement of the shares underlying these restricted stock units, as the case may be, in accordance with their respective terms, these shares may be resold freely, subject to restrictions imposed on our affiliates under Rule 144. If significant sales of these shares occur in short periods of time, these sales could reduce the market price of our common stock. Any reduction in the trading price of our common stock could impede our ability to raise capital on attractive terms, if at all. If securities or industry analysts do not publish research or reports or publish unfavorable research about our business, our stock price and trading volume could decline. The trading market for our common stock will depend in part on the research and reports that securities or industry analysts publish about us or our business. We currently have research coverage by **one** securities and industry ~~analysts~~ **analyst** . If ~~one or more of~~ the ~~analysts~~ **analyst** who covers us downgrades our stock, our stock price would likely decline. If **this** ~~one or more of these analysts~~ **analyst** ceases coverage of our company or fails to regularly publish reports on us, interest in the purchase of our stock could decrease, which could cause our stock price or trading volume to decline. Our common stock may experience future dilution as a result of future equity offerings. In order to raise additional capital, we may in the future offer additional shares of our common stock or other securities convertible into or exchangeable for our common stock at prices that may not be the same as the price per share in previous offerings. We may sell shares or other securities in any other offering at a price per share that is less than the price per share paid by investors in previous offerings, and investors purchasing shares or other securities in the future could have rights superior to existing stockholders. The price per share at which we sell additional shares of our common stock, or securities convertible or exchangeable into common stock, in future transactions may be higher or lower than the price per share paid by investors. Our business could be negatively affected as a result of the actions of activist stockholders. Proxy contests have been waged against many companies in the biopharmaceutical industry, including us, over the last several years. If faced with a proxy contest or other type of shareholder activism, we may not be able to respond successfully to the contest or dispute, which would be disruptive to our business. Even if we are successful, our business could be adversely affected by a proxy contest or shareholder dispute involving us for several reasons, including, among others: • responding to proxy contests and other actions by activist stockholders can be costly and time- consuming, disrupting operations and diverting the attention of management and employees; • perceived uncertainties as to future direction may result in the loss of potential acquisitions, collaborations or in-licensing opportunities, and may make it more difficult to attract and retain qualified personnel and business partners; and • if individuals are elected to our board of directors with a specific agenda, it may adversely affect our ability to effectively and timely implement our strategic plan and create additional value for our stockholders. These actions could cause our stock price to experience periods of volatility. Anti- takeover provisions in our charter and bylaws and under Delaware law, and the adoption of a rights plan, could prevent or delay a change in control of our company. We are a Delaware corporation and the anti- takeover provisions of Section 203 of the Delaware General Corporation Law may discourage, delay or prevent a change in control by prohibiting us from engaging in a business combination with an interested stockholder for a period of three years after the person becomes an interested stockholder, even if a change of control would be beneficial to our existing stockholders. In addition, our amended and restated certificate of incorporation and bylaws may discourage, delay or prevent a change in our management or control over us that stockholders may consider favorable. Our amended and restated certificate of incorporation and bylaws: • authorize the issuance of " blank check " preferred stock that could be issued by our board of directors to thwart a takeover attempt; • do not provide for cumulative voting in the election of directors, which would allow holders of less than a majority of the stock to elect some directors; • establish a classified board of directors, as a result of which the successors to the directors whose terms have expired will be elected to serve from the time of election and qualification until the third annual meeting following their election; • require that directors only be removed from office for cause; • provide that vacancies on the board of directors, including newly created directorships, may be filled only by a majority vote of directors then in office; • limit who may call special meetings of stockholders; • prohibit stockholder action by written consent, requiring all actions to be taken at a meeting of the stockholders; and • establish advance notice requirements for nominating candidates for election to the board of directors or for proposing matters that can be acted upon by stockholders at stockholder meetings. Our board of directors previously adopted a rights agreement, the provisions of which could have had the effect of discouraging, delaying or preventing a change in ~~or~~ management or control over us. While there is no plan to do so at this time, our board of directors may choose to adopt a new rights plan in the future. Changes to tax regulations to which we are subject could adversely affect us. We are subject to tax laws, treaties and regulations in the countries in which we operate, and these laws and treaties are subject to interpretation. New legislation or regulation that 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. We have taken, and will continue to take, tax positions based on our interpretation of such tax laws. 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 our actual financial results to deviate from previous estimates. 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; • **asset purchases; •** 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 **. It is too early to tell whether our December 2023 acquisition of PONVORY ® from Janssen will yield the results that we expect. If we experience difficulties integrating PONVORY ® into our portfolio of approved products, or we are unable to achieve market acceptance of PONVORY ®, our business and results of operations may be materially harmed** . 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 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 and are affected by numerous factors, including: • product sales; • cost of product sales; • the rate at which third- party payors approve coverage for our products; • 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. 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. Our internal computer systems, or those of our collaborators, CROs or other contractors or consultants, may fail or suffer security breaches, which could result in a material disruption of development programs for our product candidates. Despite the implementation of security measures, our internal computer systems and those of our collaborators, CROs, and other contractors and consultants are vulnerable to damage from computer viruses, unauthorized access, natural disasters, terrorism, war and telecommunication and electrical failures. Information security risks have significantly increased in recent years in part due to the proliferation of new technologies and the increased sophistication and activities of organized crime, hackers, terrorists and other external parties, including foreign state actors. As cyber threats continue to evolve, we may be required to expend significant additional resources to continue to modify or enhance our protective measures or to investigate and remediate any information security breaches. While we have not experienced any such system failure, accident or security breach to date, if such an event were to occur and cause interruptions in our operations, it could result in a material disruption of our independent drug development programs. For example, the loss of clinical trial data from ongoing or future clinical trials for any of our product candidates could result in delays in regulatory approval efforts and significantly increase costs to recover or reproduce the data. Our information security systems are also subject to laws and regulations requiring that we take measures to protect the privacy and security of certain information we gather and use in our business. For example, ~~HIPAA and its implementing regulations impose, among other requirements, certain regulatory and contractual requirements regarding the privacy and security of personal health information. In addition to HIPAA, numerous other~~ federal and state laws, including, without limitation, state security breach notification laws, state health information privacy laws and federal and state consumer protection laws, govern the collection, use, disclosure and storage of personal information. To the extent that any disruption or security breach were to result in a loss of or damage to data or applications, or inappropriate disclosure of confidential or proprietary information or personal health information, we could incur substantial liability, our reputation would be damaged, and the further development of our product candidates could be delayed.